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NOVEL COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

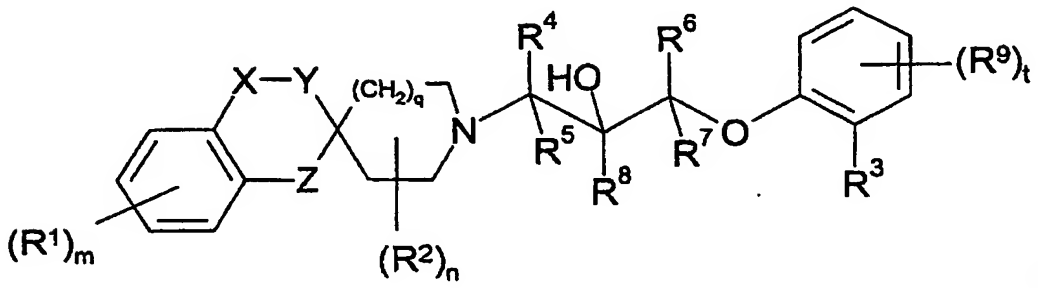
Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C) and Cys-Cys (C-C) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

In accordance with the present invention, there is therefore provided a compound of formula



(I)

wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or sulphonamido ($-SO_2NH_2$);

either X represents a bond, $-CH_2-$, -O- or -C(O)- and Y represents a bond, $-CH_2-$, -O- or -C(O)-, or X and Y together represent a group $-CH=C(CH_3)-$ or $-C(CH_3)=CH-$, and Z represents a bond, -O-, -NH- or $-CH_2-$, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent –O- or -C(O)-;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1-C_6 alkyl;

q is 0 or 1;

R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

t is 0, 1 or 2;

each R^9 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, or C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl;

R^{10} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{13}, or

R^{10} represents a group $-NR^{14}R^{15}$ or $-O-R^{16}$;

R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted with at least one substituent selected from halogen, methyl and trifluoromethyl, or
(iii) a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from halogen, amino (-NH_2), hydroxyl, trifluoromethyl, carboxyl, C_1-C_6 alkoxycarbonyl and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted with at least one substituent selected from halogen, methyl and trifluoromethyl, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally further comprising a ring oxygen atom, the heterocyclic ring being optionally substituted with at least one substituent selected from hydroxyl and C_1-C_6 alkoxy;

R^{12a} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{13} represents a C_1-C_6 alkyl, amino (-NH_2) or phenyl group;

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10}, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle; and

R^{16} represents a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10};

or a pharmaceutically acceptable salt or solvate thereof.

In the context of the present specification, an alkyl or alkenyl substituent group or an alkyl moiety in a substituent group may be linear or branched. A haloalkyl substituent group will comprise at least one halogen atom, e.g. one, two, three or four halogen atoms. In the ring substituted by R^2, R^2 may be attached to any suitable ring carbon atom including the carbon atom of $(CH_2)_q$. When R^{11} and R^{12} represent a 4- to 7-membered saturated heterocycle, it should be understood that the heterocycle will contain no more than two ring heteroatoms: the nitrogen ring atom to which R^{11} and R^{12} are attached and optionally an oxygen ring atom. When R^{14} and R^{15} represent a 4- to 7-membered saturated heterocycle, it should be understood that the only ring heteroatom present is the nitrogen atom to which R^{14} and R^{15} are attached. In the definition of R^{10} (or R^{14}, R^{15} or R^{16}) it should be noted that the saturated or unsaturated 5- to 10-membered heterocyclic ring system may have alicyclic or aromatic properties. Similarly, in the definition of R^{11} or R^{12}, a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom may have alicyclic or aromatic properties.

In an embodiment of the invention, m is 0 or 1.

Each R^1 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, hydroxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy) or sulphonamido.

In an embodiment of the invention, each R^1 independently represents halogen or C_1-C_6, preferably C_1-C_4, alkyl.

Combinations of X and Y of particular interest include any one or more of the following:

X	Y
bond	O
O	bond
CH_2	O
O	CH_2
C(O)	O
O	C(O)
CH_2	CH_2
-CH=C(CH_3)-	

In an embodiment of the invention, Z represents a bond, -O- or $-CH_2-$.

Combinations of X, Y and Z of particular interest include any one or more of the following:

X	Y	Z
bond	O	CH_2
O	bond	CH_2
CH_2	O	bond
O	CH_2	bond
C(O)	O	bond
O	C(O)	bond
CH_2	CH_2	bond
bond	O	O
O	bond	O
-CH=C(CH_3)-		bond

Each R^2 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine) or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^3 represents $-NHC(O)R^{10}$.

In another embodiment of the invention, R^3 represents $-C(O)NR^{11}R^{12}$.

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl).

In an embodiment of the invention, R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a methyl group.

In another embodiment of the invention, R^4, R^5, R^6 and R^7 each represent a hydrogen atom and R^8 represents a methyl group.

In an embodiment of the invention, t is 0 or 1.

Each R^9 independently represents halogen (e.g. chlorine, fluorine, bromine or iodine), cyano, hydroxyl, C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, haloalkyl (e.g. trifluoromethyl), or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents) independently selected from carboxyl and C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl).

In an embodiment of the invention, each R^9 independently represents halogen, cyano, hydroxyl, C_1-C_6, preferably C_1-C_4, alkoxy, C_1-C_6, preferably C_1-C_4, haloalkyl or C_1-C_6, preferably C_1-C_4, alkyl.

In another embodiment of the invention, each R^9 independently represents halogen, hydroxyl, C_1-C_4 alkoxy or C_1-C_4 haloalkyl.

R^{10} may represent a group C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_2-C_6, preferably C_2-C_4, alkenyl, C_3-C_6 cycloalkyl (cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and $-NHC(O)-R^{13}$.

The saturated or unsaturated 5- to 10-membered heterocyclic ring system in R^{10} may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

In an embodiment of the invention, R^{10} represents a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 6-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one or two ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one, two, three or four substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6, preferably C_1-C_4, alkyl, C_1-C_6, preferably C_1-C_4, alkoxy, C_1-C_6, preferably C_1-C_4, alkylthio, C_1-C_6, preferably C_1-C_4, alkylcarbonyl, C_1-C_6, preferably C_1-C_4, alkoxycarbonyl, phenyl and -NHC(O)-R^{13}.

In another embodiment of the invention, R^{10} represents a group C_1-C_6 alkyl, phenyl or an unsaturated 5- to 6-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one or two ring heteroatoms independently) selected from nitrogen and oxygen, each of which (i.e. each of the recited groups and the ring system) may be optionally substituted by one or two substituents independently selected from halogen, C_1-C_6, preferably C_1-C_4, alkyl and C_1-C_6, preferably C_1-C_4, alkoxy.

Alternatively, R^{10} may represent a group $-NR^{14}R^{15}$ or $-O-R^{16}$.

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group (i.e. each of the recited groups including the ring system) being optionally substituted as defined above for R^{10} (that is, optionally substituted with one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or

n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{13}),
or R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle (e.g. pyrrolidinyl or piperidinyl).

In R^{14} or R^{15}, the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

R^{16} represents a hydrogen atom, or a group C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, each group (i.e. each of the recited groups including the ring system) being optionally substituted as defined above for R^{10} (that is, optionally substituted with one or more (e.g. one, two, three or four) substituents independently selected from nitro, hydroxyl, oxo, halogen (e.g. fluorine, chlorine, bromine or iodine), carboxyl, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylthio (e.g. methylthio or ethylthio), C_1-C_6, preferably C_1-C_4, alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, n-pentylcarbonyl or n-hexylcarbonyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), phenyl and -NHC(O)-R^{13}).

In R^{16}, the saturated or unsaturated 5- to 10-membered heterocyclic ring system may be monocyclic or polycyclic (e.g. bicyclic), examples of which include pyrrolidinyl, piperidinyl, pyrazolyl, thiazolidinyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, quinolinyl, benzimidazolyl, triazolyl, tetrazolyl, pyridinyl and combinations of any two or more thereof.

R^{11} and R^{12} each independently represent (i) a hydrogen atom,

(ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two or three ring heteroatoms independently) selected from nitrogen, oxygen and sulphur (examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, thienyl, furanyl and combinations of any two or more thereof), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), methyl and trifluoromethyl, or

(iii) a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), amino, hydroxyl, trifluoromethyl, carboxyl, C_1-C_6, preferably C_1-C_4, alkoxycarbonyl and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom (e.g. one, two or three ring heteroatoms independently) selected from nitrogen, oxygen and sulphur (examples of which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, thienyl, furanyl and combinations of any two or more thereof), the ring being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), methyl and trifluoromethyl, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally further comprising a ring oxygen atom (e.g. pyrrolidinyl, piperidinyl or morpholinyl), the heterocyclic ring being optionally

substituted with at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted with at least one substituent selected from halogen, methyl and trifluoromethyl, or (iii) a C_1-C_6 alkyl group optionally substituted by amino or hydroxyl, or
R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally further comprising a ring oxygen atom, the heterocyclic ring being optionally substituted by hydroxyl.

R^{12a} represents a hydrogen atom or a C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) group.

In an embodiment of the invention, R^{12a} represents a hydrogen atom.

R^{13} represents a C_1-C_6, preferably C_1-C_4, alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), amino or phenyl group.

In an embodiment of the invention:

m is 0 or 1;

R^1 represents halogen;

either X represents a bond, $-CH_2-$, -O- or -C(O)- and Y represents a bond, $-CH_2-$, -O- or -C(O)-, or X and Y together represent a group $-CH=C(CH_3)-$, and Z represents a bond, -O- or $-CH_2-$, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent –O- or -C(O)-;

n is 0;

q is 0 or 1;

R^3 represents $-NHC(O)R^{10}$, $-C(O)NR^{11}R^{12}$ or $-COOR^{12a}$;

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a methyl group;

t is 0 or 1;

R^9 represents halogen, hydroxyl, methoxy or trifluoromethyl;

R^{10} represents methyl;

R^{11} and R^{12} each independently represent hydrogen, methyl, cyclopropyl, hydroxyethyl or aminoethyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a morpholinyl group, or form a piperidinyl group substituted by hydroxyl; and

R^{12a} represents a hydrogen atom.

Examples of compounds of the invention include:

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-[2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-(trifluoromethyl)phenyl]acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropyl-4-methoxybenzamide,

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(5-Chloro-2-{[(2S)-3-(6-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide,

N-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide,

2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide,

N-(2{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]phenyl)acetamide,

N-(4-Chloro-2-{[(2S)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-Cyclopropyl-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}benzamide,

N-(4-Chloro-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(5-Chloro-2{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-2-hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide,

N-[2-{[(2S)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-5-(trifluoromethyl)phenyl]acetamide,

N-(2-{[(2S)-2-Hydroxy-3-(2-methyl-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(2,3-Dihydro-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-2-Hydroxy-3-(2-oxo-1'*H*-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide,

2-{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-methylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxy-*N*-methylbenzamide (trifluoroacetate),

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy]oxy}-4-hydroxy-*N*-methylbenzamide,

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate,

N-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-2-methyl-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate,

N-(2-{[(2S)-3-(5-Chloro-1'H,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)benzamide,

N-(2-Aminoethyl)-2-{](2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide,

2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

N-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-[2-({(2S)-3[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide,

N-[2-({(2S)-3[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide,

N-[2-({(2S)-3-[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide,

N-[2-({(2S)-3-[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (trifluoroacetate),

3(S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

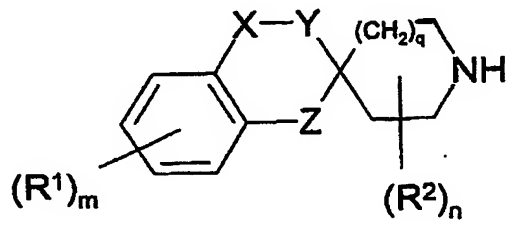
3(R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(morpholin-4-ylcarbonyl)phenol,

and pharmaceutically acceptable salts and solvates of any one thereof.

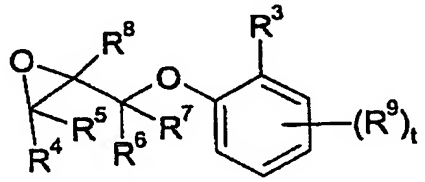
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) reacting a compound of formula



(II)

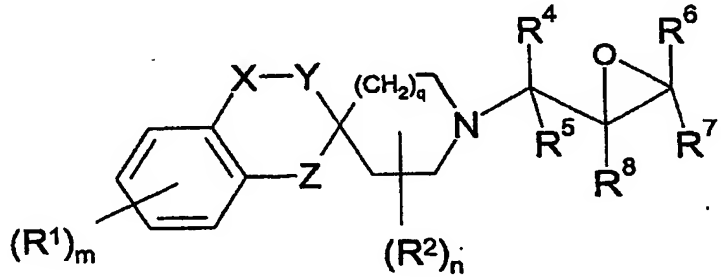
wherein m, R^1, n, R^2, q, X, Y and Z are as defined in formula (I), with a compound of formula



(III)

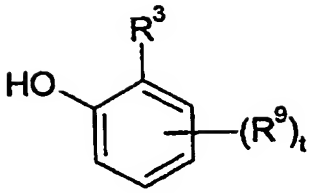
wherein R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

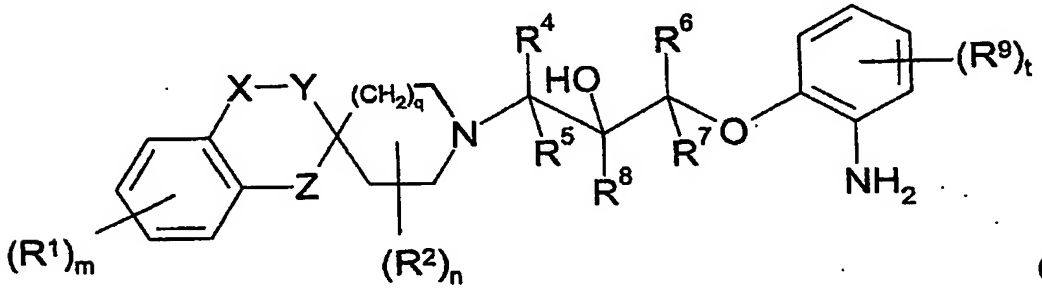
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of formula



(V)

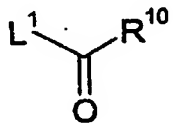
wherein R^3, t and R^9 are as defined in formula (I), in the presence of a suitable base; or

(c) when R^3 represents $-NHC(O)R^{10}$, reacting a compound of formula



(VI)

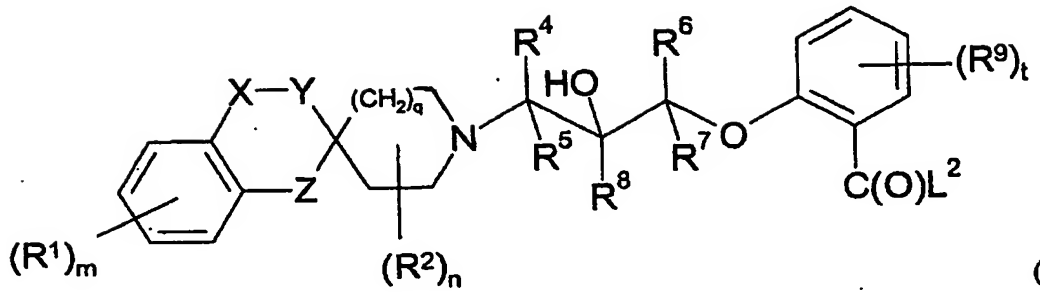
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula



(VII)

wherein L^1 represents a leaving group (e.g. a hydroxyl group or a halogen atom such as chlorine) and R^{10} is as defined in formula (I); or

(d) when R^3 represents $-C(O)NR^{11}R^{12}$, reacting a compound of formula



(VIII)

wherein L^2 represents a leaving group (e.g. a hydroxyl group or a halogen atom such as chlorine) and m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula (IX), $NHR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined in formula (I);

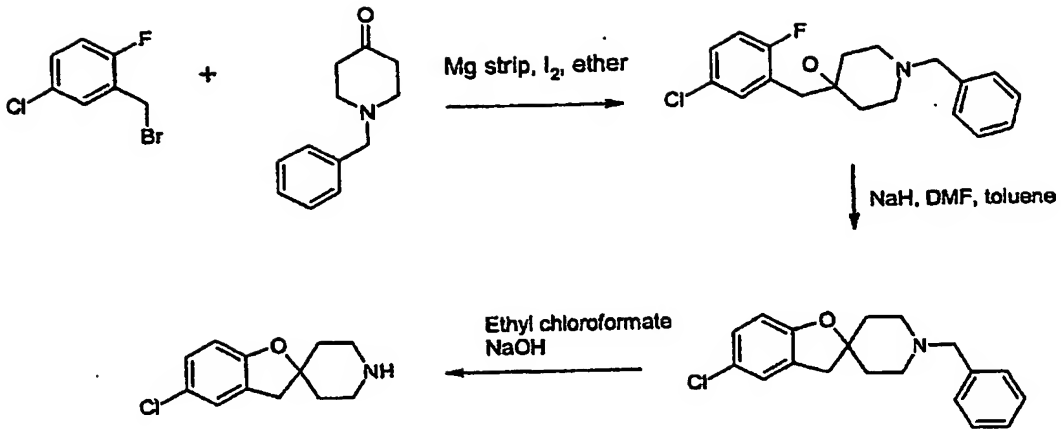
and optionally after (a), (b), (c) or (d) forming a pharmaceutically acceptable salt or solvate.

The processes of the invention may conveniently be carried out in a solvent, e.g. an organic solvent such as an alcohol (e.g. methanol or ethanol), a hydrocarbon (e.g. toluene) or tetrahydrofuran or acetonitrile at a temperature of, for example, 0°C or above such as a temperature in the range from 0, 5, 10, 15 or 20°C to 100, 110 or 120°C.

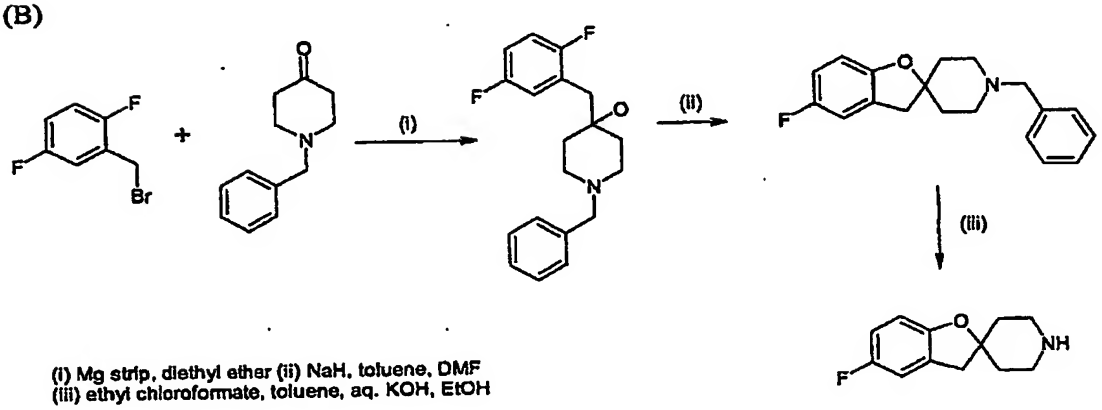
Compounds of formulae (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) are either commercially available, are known in the literature or may be prepared using known techniques.

For example, compounds of formula (II) in which m is 1, R^1 is chlorine or fluorine, n is 0, q is 1, one of X and Y represents a bond and the other of X and Y represents an oxygen atom and Z represents CH_2, may be prepared according to the following reaction schemes in which DMF denotes dimethylformamide and EtOH denotes ethanol:

(A)



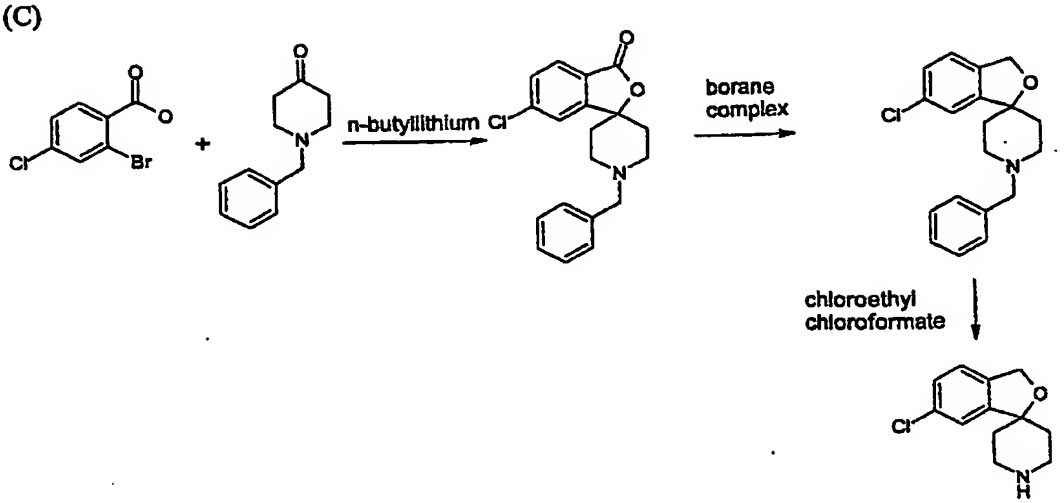
(B)



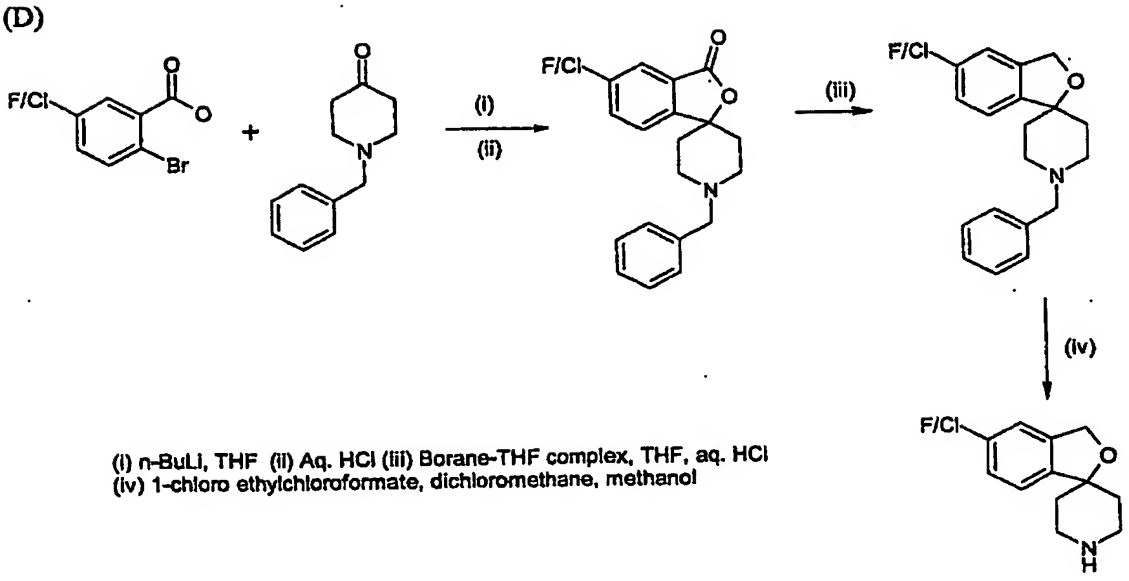
(i) Mg strip, diethyl ether (ii) NaH, toluene, DMF
(iii) ethyl chloroformate, toluene, aq. KOH, EtOH

Compounds of formula (II) in which m is 1, R^1 is chlorine or fluorine, n is 0, q is 1, X represents CH_2, Y represents an oxygen atom and Z represents a bond, may be prepared according to the following reaction schemes in which THF denotes tetrahydrofuran:

(C)



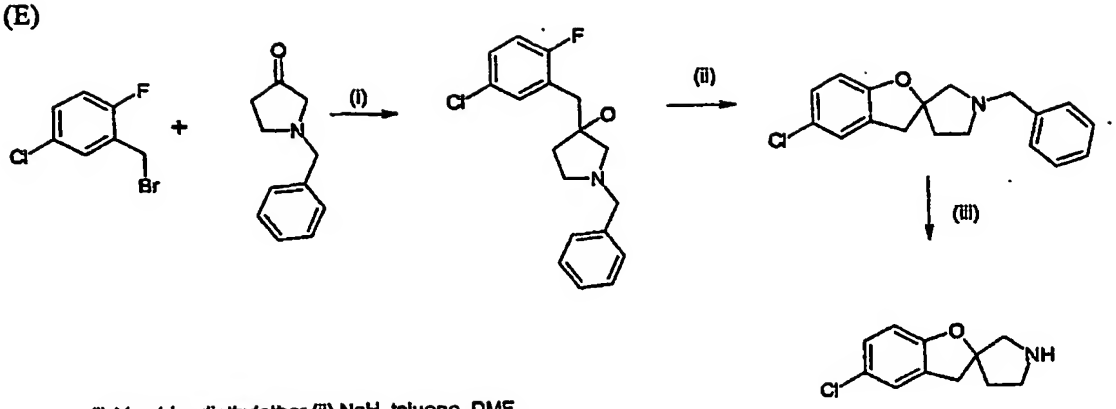
(D)



(i) n-BuLi, THF (ii) Aq. HCl (iii) Borane-THF complex, THF, aq. HCl
(iv) 1-chloro ethylchloroformate, dichloromethane, methanol

Compounds of formula (II) in which m is 1, R^1 is chlorine, n is 0, q is 0, one of X and Y represents a bond and the other of X and Y represents an oxygen atom and Z represents CH_2, may be prepared according to the following reaction scheme in which DMF denotes dimethylformamide and EtOH denotes ethanol:

(E)



(i) Mg strip, diethylether (ii) NaH, toluene, DMF
(iii) ethyl chloroformate, toluene, aq. KOH, EtOH

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the reagents may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

Compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses the use of all geometric and optical isomers (including atropisomers) of the compounds of formula (I) and mixtures thereof including

racemates. The use of tautomers and mixtures thereof also form an aspect of the present invention. Enantiomerically pure forms are particularly desired.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially MIP-1α chemokine receptor) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS).

Examples of these conditions are:

(1) **(the respiratory tract)** airways diseases including chronic obstructive pulmonary disease (COPD) such as irreversible COPD; asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness); bronchitis; acute, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis; sarcoidosis, farmer's lung and related diseases, fibroid lung and idiopathic interstitial pneumonia;

(2) **(bone and joints)** rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin)** psoriasis, atopical dermatitis, contact dermatitis and other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus, bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, Alopecia areata and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema;

(5) **(other tissues and systemic disease)** multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus, systemic lupus, erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia pupura;

(6) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(7) cancers, especially non-small cell lung cancer (NSCLC) and squamous sarcoma;

(8) diseases in which angiogenesis is associated with raised chemokine levels; and

(9) cystic fibrosis, stroke, re-perfusion injury in the heart, brain, peripheral limbs and sepsis.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention still further provides a method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I) may be in the range from 0.001 mg/kg to 30 mg/kg.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

The invention will now be further explained by reference to the following illustrative examples, in which ^{1}H NMR spectra were recorded on Varian Unity Inova 400. The central solvent peak of chloroform-*d* (δ_H 7.27 ppm) were used as internal standard. Low resolution mass spectra and accurate mass determination were recorded on a Hewlett-Packard 1100 LC-MS system equipped with APCI /ESI ionisation chambers.
All solvents and commercial reagents were laboratory grade and used as received.
The nomenclature used for the compounds was generated with ACD/IUPAC Name Pro.

Examples

Intermediate compound: 5-Chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

This compound was prepared as described by Fffland, R. C; Gardner, B. A; Strupczewski, J., *J. Heterocyclic Chem.*, **1981**, *18*, 811-814.

Intermediate compound: 6-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

(i) 1'-Benzyl-6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one

To a solution of 2-bromo-4-chlorobenzoic acid (2.35 g, 10.0 mmol) in tetrahydrofuran (THF) (15 mL) was added, a 1.6 M solution in hexane, n-butyllithium (Parham, W.E; Egberg, D. C; Sayed, Y. A; Thraikill, R. W; Keyser, G. E; William, M. N; Montgomery, M. C; Jones, L. D., *J. Org. Chem.*, 1976, *41*, 2628-2633) (20 mL, 32.0 mmol) slowly at -78 ^{0}C under nitrogen. After addition was complete the reaction mixture was stirred at -78 ^{0}C for 3 hours (h). Then a solution of 1-benzylpiperidin-4-one (3.78 g, 20.0 mmol) in THF (10 mL) was added slowly to the reaction mixture at –78 ^{0}C. After addition was complete the reaction temperature was raised to room temperature and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of water (H_2O) (60 mL) and diethyl ether (60 mL), layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL). The aqueous layer was acidified with aq 6 M HCl to pH 2 and boiled for 1 h, cooled to 0 ^{0}C, pH was adjusted to 10 by addition of aqueous sodium hydroxide (NaOH) (6M) and rapidly extracted with trichloromethane ($CHCl_3$). The organic layer was washed with H_2O, dried over sodium sulphate (Na_2SO_4), filtered and concentrated in vacuo to give sub-titled compound (1.22 g) and it was pure enough for the next step.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.84 (d, J = 8.2 Hz, 1H); 7.51 (dd, J = 1.7, 8.2 Hz, 1H); 7.45-7.25 (m, 6H); 3.67 (s, 2H); 3.00 (br.d; J = 9.4 Hz, 2H); 2.61 (br.t, J = 11.2 Hz, 2H); 2.32 (br, s, 2H); 1.74 (d, J = 12.2 Hz, 2H).
APCI-MS: m/z 328(MH^+).

(ii) 1'-Benzyl-6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]-3-one (1.1 g, 3.35 mmol) in THF (15 mL) was added 1 M solution of borane (Marxer, A; Rodriguez, H. R; McKenna, J. M; Tsai, H. M., *J. org. Chem.*, 1975, *40*, 1427-1430) complex in THF (7 mL, 7.0 mmol) slowly at 0 ^{0}C. After addition was complete, the reaction mixture was

kept at room temperature for 30 minutes (min), then kept at reflux overnight, cooled to 0 °C and 6M aqueous hydrochloric acid (HCl) (3.5 mL) was added slowly. The reaction mixture was kept at reflux for 5 h, cooled to 0 °C, pH of the reaction mixture was adjusted to 10 by addition of aqueous NaOH 6M and the whole was extracted with ethyl acetate. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the sub-titled compound (900 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.44-7.22 (m, 6H); 7.18 (m, 2H); 5.03 (s, 2H); 3.60 (s, 2H)2.87 (br.d, J = 10.5 Hz, 2H); 2.45 (br.t, J = 11.2 Hz, 2H); 2.00 (br.s, 2H); 1.79 (d, J = 11.2 Hz, 2H).
APCI-MS: m/z 314(MH^+).

(iii) 6-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (850 mg, 2.7 mmol) in dichloromethane (CH_2Cl_2) (8 mL) was added chloroethyl chloroformate (Yang, B. V; o'Rourke, D; Li, J., *Synlett*, 1993, 195-196) (772 mg, 5.4 mmol) slowly at 0 °C. After addition was complete the reaction mixture was stirred at 0 °C for 30 min. The volatiles were removed in vacuo, residue was dissolved in methanol (10 mL) and kept at reflux for 40 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-6% methanol in dichloromethane, 0.2% ammonium hydroxide (NH_4OH)) to give the titled compound (170 mg) and 1'-benzyl-6-chloro-3H-spiro[2-benzofuran-1,4'-piperidine] was recovered (200 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.29-7.21 (m, 3H); 5.00 (s, 2H); 2.99 (m, 4H); 1.90-181 (m, 2H); 1.70 (m, 2H).
APCI-MS: m/z 224(MH^+).

Intermediate compound: 5-Fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

(iv) 1'-Benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one

This reaction was performed as described for (i) above using 2-bromo-5-fluorobenzoic acid (2.19 g, 10.0 mmol), 1-benzylpiperidin-4-one (3.78 g, 20.0 mmol), n-butyl lithium (n-BuLi) (20 mL) and THF (20 mL) to give the sub-titled compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.58-7.23 (m, 8H); 3.68 (s, 2H); 2.98 (m, 2H); 2.59 (m, 2H); 2.28 (m, 2H); 1.74 (m, 2H).

APCI-MS: m/z 312(MH^+).

(v) 1'-Benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

This reaction was performed as described for (ii) above using 1'-benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one (200 mg, 0.642 mmol), borane THF complex 1M solution (1,34 mL, 1.34 mmol) and THF (3 mL) to give the sub-titled compound (148 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.41-7.27 (m, 5H); 7.08 (dd, J = 4.8, 8.3 Hz, 1H); 6.97 (m, 1H); 6.89 (m, 1H); 5.08 (s, 2H); 3.60 (s, 2H); 2.87 (m, 2H); 2.46 (m, 2H); 1.97 (m, 2H); 1.88 (m, 2H).

APCI-MS: m/z 298(MH^+).

(vi) 5-Fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

This reaction was performed as described for (iii) above using 1'-benzyl-5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (145 mg, 0.487 mmol), chloroethyl chloroformate (0.07 mL) to give the titled compound.

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.18 (dd, J = 4.9, 8.1 Hz, 1H); 7.03-6.96 (m, 2H); 5.01 (s, 2H); 3.09-2.93 (m, 4H); 1.91-1.81 (m, 2H); 1.73-1.66 (m 2H).

APCI-MS: m/z 208(MH^+).

Example 1

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

Step I:

***N*-{2-[(2S)-Oxiran-2-ylmethoxy]phenyl}acetamide**

A mixture of *N*-(2-hydroxyphenyl)acetamide (1.51g, 10 mmol), (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (2.59 g, 10 mmol) and cesium carbonate (Cs_2CO_3) (3.9 g, 12 mmol) in dimethylformamide (DMF) (30 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and H_2O. The organic layer was dried over Na_2SO_4, filtered, concentrated and the residue was purified by silica gel flash chromatography to give the subtitled compound (1.34 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.40 (m, 1H); 7.90 (br.,s, 1H); 7.05 (m, 2H); 6.92 (m, 1H); 4.37 (dd, J = 2.5, 11.3 Hz, 1H); 3.98 (dd, J = 5.9, 11.3 Hz, 1H); 3.40 (m, 1H); 2.97 (t, J = 4.8 Hz, 1H); 2.81 (dd, J = 2.7, 4.8 Hz, 1H); 2.20 (s, 3H).

Step II:

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (36 mg, 0.16 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (33 mg, 0.16 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane containing 0.2% ammonium hydroxide) to give the titled compound (25 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, J = 4.8 Hz, 1H); 7.22 (m, 1H); 7.13 (m, 2H); 7.05 (d, J = 7.5 Hz, 1H); 6.98 (m, 1H); 6.74 (d, J = 8.6 Hz, 1H); 4.49 (m, 1H); 4.08 (d, J = 4.8 Hz, 2H); 3.70 (m, 2H); 3.43 (m, 4H); 3.12 (s, 2H); 2.20 (m, 7H).

APCI-MS: m/z 433 (MH^+).

Example 2

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide**

Step I:

***N*-(4-Fluoro-2-hydroxyphenyl)acetamide**

A mixture of 5-fluoro-2-nitrophenol (5 g, 31.8 mmol), acetic anhydride (4.86 g, 47.7 mmol) and platinum on carbon (5%, 200 mg) in methanol was hydrogenated at 35 psi for 3 hours. The catalyst was filtered off and the residue was purified by silica gel flash chromatography to give the subtitled compound (4.7 g).

^{1}H-NMR (CD_3OD, 300 MHz): δ 7.56-7.51 (m, 1H); 6.61-6.50 (m, 2H); 2.15 (s, 3H).
APCI-MS: m/z 170 (MH^+).

Step II:

***N*-{4-Fluoro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide**

A mixture of *N*-(4-fluoro-2-hydroxyphenyl)acetamide (1.69 g, 10.0 mmol), (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (2.59 g, 10.0 mmol) and Cs_2CO_3 (4.87 g, 15.0 mmol) in DMF (15 mL) was stirred at room temperature for 2 h. The reaction mixture was partitioned between ethylacetate and H_2O. The organic layer was dried over Na_2SO_4 filtered and concentrated. The residue was purified by silica gel flash chromatography to give the subtitled compound (1.35 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.33-8.29 (m, 1H); 7.71 (br. S, 1H), 6.74-6.66 (m, 2H); 4.39-4.36 (m, 1H); 3.95-3.90 (m, 1H); 3.41-3.39 (m, 1H); 2.99-2.97 (m, 1H); 2.80-2.79 (m, 1H).
APCI-MS: m/z 226 (MH^+).

Step III:

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (45 mg, 0.201 mmol) and *N*-{4-fluoro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (45.3 mg, 0.201 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (33 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.52 (s, 1H); 8.20 (dd, *J* = 6.4, 8.9 Hz, 1H); 7.18 (s, 1H); 7.13 (dd, *J* = 2.0, 8.5 Hz, 1H); 6.74 (dd, *J* = 2.6, 8.6 Hz, 1H); 6.69 (d, *J* = 8.6 Hz, 1H); 6.59 (dd, *J* = 2.6, 9.8 Hz, 1H); 4.48 (m, 1H); 4.17 (dd, *J* = 3.7, 9.8 Hz, 1H); 4.00 (dd, *J* = 2.2, 9.8 Hz, 1H); 3.79 (m, 2H); 3.59 (br.d, *J* = 11.7 Hz, 1H); 3.38 (m, 1H); 3.27 (m, 1H); 3.12 (s, 2H); 3.05 (m, 1H); 2.48 (m, 1H); 2.37 (m, 1H); 2.24 (s, 3H); 2.17 (m, 2H).

APCI-MS: m/z 451 (MH^+).

Example 3

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide**

Step I:

***N*-(2-Hydroxy-4 methoxyphenyl)acetamide**

2-Nitro-5-methoxyphenol (prepared from 3-methoxyphenol, R. J. Maleski, *Synthetic Communications*, **1993**, *23*, 343-348) (48.5g,0.287 mol) dissolved in THF (1.5 L) was hydrogenated at ambient temperature over night with 10% palladium on carbon (10 g) until 20.3 L of hydrogen was consumed. After filtration and evaporation the residue was suspended in degased water (1.7 L) and acetic anhydride (42.5 mL) was added with stirring. The mixture was heated to 60 °C for 1h and then cooled to room temperature. The volatiles were removed in vacuo and the solid was washed thoroughly with water and dried in vacuo to give brick-red crystals (41.7 g, 80 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H); 7.34 (br.s, 1H); 6,81 (d, 1H); 6.58 (d, 1H); 6.44 (dd, 1H); 3.78 (s, 3H); 2,26 (s, 3H)

Step II:

***N*-{4-Methoxy-2[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide**

N-(2-Hydroxy-4-methoxyphenyl)acetamide (18.12 g, 0.1 mol) and S-(+)-glycidylnosylate (25.92 g, 0.1 mol) were dissolved in dry DMF (75 mL) and stirred under nitrogen (N_2) on an ice-bath. Cesium carbonate (35.8g, 0.11mol) was added and the stirring under N_2 was continued at ambient temperature overnight. The mixture was poured into ethyl acetate (1L) and water (250 mL). The organic phase was washed with water (3 x 250 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give an orange solid crude product (29 g), which was recrystallized from ethanol (100 mL) and washed with ether to give white crystals. More white crystals were obtained from the mother liquor, after evaporation and recrystillazition from 2-propanol. Total yield 15 g (63%).

^{1}H-NMR ($CDCl_3$): δ 8.22 (d, 1H); 7.64 (bs, 1H); 6.53 (dd, 1H); 6.50 (d, 1H); 4.34 (dd, 1H); 3.92 (dd, 1H); 3.79 (s, 3H); 3.38 (m, 1H); 2.96 (t, 1H); 2.78 (dd, 1H); 2.20 (s, 3H)

Step III:

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (200 mg, 0.894 mmol) and *N*-{4-methoxy-2[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (212 mg, 0.894 mmol) in ethanol (5 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (400 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.74 (d, J = 8.9 Hz, 1H); 7.13 (m, 1H); 7.04 (dd, J = 2.3, 8.5 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 6.61 (d, J = 2.7 Hz, 1H); 6.51 (dd, J = 2.7, 8.8 Hz,

1H); 4.17 (m, 1H); 4.08 (dd, J = 3.4, 10.0 Hz, 1H); 3.98 (dd, J = 6.3, 9.9 Hz, 1H); 3.79 (s, 3H); 3.03 (s, 2H); 2.72 (m, 4H); 2.62 (m, 2H); 2.15 (s, 3H); 1.95 (m, 2H); 1.84 (m, 2H). APCI-MS: m/z 461 (MH^+).

Example 4

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide**

To a cold (0 ^{0}C) solution of *N*-(2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide (380 mg, 0.82 mmol) in dichloromethane (8 mL) was added 1M solution of boron tribromide (BBr_3) in dichloromethane (2.47 mL, 2.47 mmol) slowly. After addition was complete the icebath was removed and the reaction mixture was stirred at room temperature for 2 h 30 min. The reaction mixture was cooled to 0 ^{0}C and methanol (2 mL) was added slowly with stirring for 10 min. The volatiles were removed in vacuo. The residue was dissolved in large volume of ethyl acetate, washed successively with aqueous sodium hydrogencarbonate ($NaHCO_3$) solution and water. The organic layer was dried over Na_2SO4, filtered, concentrated and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (155 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.57 (d, J = 8.7 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, J = 2.3, 8.5 Hz, 1H); 6.66 (d, J = 8.5 Hz, 1H); 6.48 (d, J = 2.5 Hz, 1H); 6.32 (dd, J = 2.5, 8.6 Hz, 1H); 4.17 (m, 1H); 4.06 (dd, J = 3.4, 9.8 Hz, 1H); 3.93 (dd, J = 6.2, 9.8 Hz, 1H); 3.03 (s, 2H); 2.70 (m, 4H); 2.59 (m, 2H); 2.13 (s, 3H); 1.95 (m, 2H); 1.84 (m, 2H).
APCI-MS: m/z 447 (MH^+).

Example 5

***N*-[2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-(trifluoromethyl)phenyl]acetamide**

Step I:

***N*-[2-{[(2S)-2-Methyloxiran-2-yl]methoxy}-5-(trifluoromethyl)phenyl] acetamide**

A mixture of 2-nitro-4-(trifluoromethyl)phenol (310 mg, 1.5 mmol), palladium on carbon (10%, 125 mg) and acetic anhydride (306.3 mg, 3.0 mmol) in methanol was hydrogenated for 2 h at atmospheric pressure. The catalyst was filtered off, the filtrate was concentrated in vacuo to give crude *N*-[2-hydroxy-5-(trifluoromethyl)phenyl]acetamide (331mg). A part (219.16 mg, 1.0 mmol) of *N*-[2-hydroxy-5-(trifluoromethyl)phenyl]acetamide was treated with [(2S)-2-methyloxiran-2-yl]methyl3-nitrobenzenesulfonate (273.27 mg, 1.0 mmol) in the presence of Cs_2CO_3 (406.25 mg, 1.25 mmol) in DMF (5 mL) at room temperature for 5 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered, concentrated. The residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (230 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.86 (s, 1H); 8.00 (br.s, 1H); 7.29 (m, 1H); 6.97 (d, J = 8.5 Hz, 1H); 4.23 (d, J = 11.0 Hz, 1H); 4.04 (d, J = 11.03 Hz, 1H) 2.93 (m, 1H); 2.81 (d, J = 4.6 Hz, 1H); 2.22 (s, 31H); 1.42 (s, 3H).

Step II:

***N*-[2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-(trifluoromethyl)phenyl]acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (35 mg, 0.155 mmol) and *N*-[2-{[(2S)-2-methyloxiran-2-yl]methoxy}-5-(trifluoromethyl)phenyl] acetamide (45 mg, 0.155 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (28 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 8.40 (d, J = 1.8 Hz, 1H); 7.40 (dd, J = 1.4, 8.7 Hz, 1H); 7.18 (d, J = 8.6 Hz, 1H); 7.13 (m, 1H); 7.03 (dd, J = 2.2, 8.5 Hz, 1H); 6.63 (d, J = 8.5 Hz,

1H); 4.13 (d, J = 9.3 Hz, 1H); 3.98 (d, J = 9.3 Hz, 1H); 2.99 (s, 2H); 2.78 (m, 1H); 2.68 (m, 3H); 2.58 (m, 1H); 2.22 (s, 3H); 1.88 (m, 2H); 1.78 (m, 2H); 1.32 (s, 3H).
APCI-MS: m/z 513 (MH^+).

Example 6

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropylbenzamide

Step I:

***N*-Cyclopropyl-2-hydroxybenzamide**

A mixture of of methyl salicylate (4.36 g, 28.69 mmol) and cyclopropylamine (1.64 g) was heated in a sealed tube at 80-100 ^{0}C for 3h. An additional 0.5 g of cyclopropylamine was added and heated at 70 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography to give the subtitled compound (2.71 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 12.40 (s, 1H); 7.40 (m, 1H); 7.38 (m, 1H); 7.01 (m, 1H); 6.81 (m, 1H); 6.48 (br.s, 1H); 2.85 (m, 1H); 0.98 (m, 2H); 0.82 (m, 2H).

Step II:

***N*-Cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide**

A mixture of *N*-cyclopropyl-2-hydroxybenzamide (270 mg, 1.52 mmol), (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (378 mg, 1.68 mmol) and cesium carbonate (645 mg, 1.98 mmol) in DMF (4 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (40% heptane in ethyl acetate) to give the subtitled compound (354 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.22 (dd, J = 1.8, 7.8 Hz, 1H); 7.95 (br.s, 1H); 7.42 (m, 1H); 7.10 (m, 1H); 6.93 (d, J = 8.3 Hz, 1H); 4.44 (dd, J = 2.5, 10.7 Hz, 1H); 4.08 (dd, J =

5.1, 10.8 Hz, 1H); 3.40 (m, 1H); 3.04-2.95 (m, 2H); 2.83 (dd, J = 2.7, 4.5 Hz, 1H); 0.86 (m, 2H); 0.65 (m, 2H).

Step III:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (9 mg, 0.04 mmol) and *N*-cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (9.4 mg, 0.4 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (7 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.92 (m, 1H); 7.47 (m, 1H); 7.13 (m, 2H); 7.05 (m, 2H); 6.65 (d, J = 8.5 Hz, 1H); 4.23 (dd, J = 3.0, 9.4 Hz, 1H); 4.16 (m, 1H); 4.09 (dd, J = 5.5, 9.4 Hz, 1H); 3.03 (s, 2H); 2.93 (m, 1H); 2.70 (br. S, 4H); 2.60 (d, J = 6.3 Hz, 1H); 1.96 (m, 2H); 1.85 (m, 2H); 0.81 (m, 2H); 0.69 (m, 2H).
APCI-MS: m/z 457 (MH^+).

Example 7

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide

Step I:

***N*-Cyclopropyl-4-fluoro-2-hydroxybenzamide**

A suspension of methyl 4-fluoro-2-hydroxybenzoate (510 mg, 3.0 mmol) in cyclopropylamine (5 mL) was stirred at room temperature overnight when it became a clear solution. The volatiles were removed in vacuo and the residue was purified by silics gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the subtitled compound (493 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 12.65 (s, 1H); 7.28 (m, 1H); 6.69 (dd, J = 2.6, 10.4 Hz, 1H); 6.56 (ddd, J = 2.6, 8.0, 10.4 Hz, 1H); 6.30 (br. S, 1H); 2.88 (m, 1H); 0.98 (m, 2H); 0.66 (m, 2H).

APCI-MS: m/z 196 (MH^+).

Step II:

***N*-Cyclopropyl-4-fluoro-2-(oxiran-2-ylmethoxy)benzamide**

A mixturte of *N*-cyclopropyl-4-fluoro-2-hydroxybenzamide (195 mg, 1.0 mmol), (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (259 mg, 1.0 mmol) and Cs_2CO_3 (390 mg, 1.2 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-30% ethylacetate in petroleum ether) to give the subtitled compound (150 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, J = 7.0, 8.8 Hz, 1H); 7.80 (br. s, 1H); 6.82 (ddd, J = 2.3, 7.6, 10.2 Hz, 1H); 6.66 (dd, J = 2.3, 10.2 Hz, 1H); 4.45 (dd, J = 2.4, 10.7 Hz, 1H); 4.05 (dd, J = 5.1, 10.7 Hz, 1H); 3.40 (m, 1H); 3.00 (m, 2H); 2.84 (dd, J = 2.6, 4.8 Hz, 1H); 0.86 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 252 (MH^+).

Step III:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropyl-4-fluorobenzamide

A mixturte of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (30 mg, 0.134 mmol) and *N*-cyclopropyl-4-fluoro-2-(oxiran-2-ylmethoxy)benzamide (33.6 mg, 0.134 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (36 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.97 (dd, J = 6.9, 8.7 Hz, 1H); 7.14 (m, 1H); 7.05 (dd, J = 2.3, 8.5 Hz, 1H); 6.96 (dd, J = 2.4, 10.4 Hz, 1H); 6.82 (ddd, J = 2.4, 8.0, 10.4 Hz, 1H); 6.66 (d, J = 8.5 Hz, 1H); 4.24 (dd, J = 3.0, 9.4 Hz, 1H); 4.17 (m, 1H); 4.10 (dd, J = 5.5, 9.4 Hz, 1H); 3.05 (s, 2H); 2.82 (m, 1H); 2.71 (br. s, 4H); 2.60 (d, J = 6.3 Hz, 2H); 1.99 (m, 2H); 1.88 (m, 2H); 0.83 (m, 2H); 0.58 (m, 2H).

APCI-MS: m/z 252 (MH^+).

Example 8

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropyl-4-methoxybenzamide

Step I:

***N*-Cyclopropyl-2-hydroxy-4-methoxybenzamide**

A suspension of methyl 2-hydroxy-4-methoxybenzoate (5.1 g, 28.0 mmol) in cyclopropyl amine 24 mL) was stirred at room temperature for 5 days. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-60% ethyl acetate in petroleum ether) to give the subtitled compound (1.8 g).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.61 (d, J = 8.8 Hz, 1H); 6.42 (m, 2H); 3.80 (s, 3H); 2.80 (m, 1H); 0.80 (m, 2H); 0.62 (m, 2H).

APCI-MS: m/z 208 (MH^+)

Step II:

***N*-Cyclopropyl-4-methoxy-2-[(2S)-oxiran-2-ylmethoxy]benzamide**

A mixture of *N*-cyclopropyl-2-hydroxy-4-methoxybenzamide (700 mg, 3.38 mmol), (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (876 mg, 3.38 mmol) and Cs_2CO_3 (1.31 g, 4.05 mmol) in DMF (12 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash

chromatography (0-80% ethyl acetate in petroleum ether) to give the subtitled compound (1.0 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 8.8 Hz, 1H); 7.85 (br.s, 1H). 6.63 (dd, J = 2.3, 8.8 Hz, 1H); 6.45 (d, J = 2.3 Hz, 1H); 4.42 (dd, J = 2.5, 10.8 Hz, 1H); 4.05 (dd, J = 5.2, 10.8 Hz, 1H); 3.82 (s, 3H); 3.40 (m, 1H); 3.00 (m, 2H); 2.83 (dd, J = 2.6, 4.8 Hz, 1H); 0.88 (m, 2H); 0.68 (m, 2H).
APCI-MS: m/z 264 (MH^+).

Step III:
2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-methoxybenzamide
A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (100 mg, 0.447 mmol) and *N*-cyclopropyl-4-methoxy-2-[(2S)-oxiran-2-ylmethoxy]benzamide (117.7 mg, 0.447 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatograpy (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (145 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.18 (m, 2H); 7.12 (m, 1H); 7.09 (dd, J = 2.3, 8.5 Hz, 1H); 6.70 (d, J = 8.5 Hz, 1H); 6.63 (dd, J = 2.3, 8.8 Hz, 1H); 6.44 (d, J = 2.3 Hz, 1H); 4.19 (dd, J = 3.3, 9.4 Hz, 1H); 4.13 (m, 1H); 3.97 (dd, J = 5.0, 9.4 Hz, 1H); 3.88 (s, 3H); 3.02 (m, 3H); 2.92 (m, 1H); 2.81 (m, 1H); 2.63 (m, 3H); 2.53 (dd, J = 3.6, 12.4 Hz, 1H); 2.04 (m, 2H); 1.88 (m, 2H); 0.85 (m, 2H); 0.06 (m, 2H).
APCI-MS: m/z 487 (MH^+).

Example 9

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

Step I:

2-Methyl-1,3-benzoxazol-6-ol

To a stirred solution of 1-(2,4-dihydroxyphenyl)ethanone (20 g, 131 mmol) in pyridine (80 mL) hydroxylamine hydrochloride (9.1 g, 131 mmol) was added over a period of 15 min in small portions at room temperature. The reaction mixture was stirred for 20 h and then diluted with water (600 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with water (2 x 250 mL) and 5 % aqueous HCl (250 mL). The solvent was removed in vacuo. Water (200 mL) was addded to the residue and then concentrated in vacuo, then toluene (200 mL) was added and concentrated in vacuo. The residue was dissolved in a mixture of acetonitrile (150 mL) and dimethylacetamide (25 mL). The solution was cooled to 5 °C, phosphorus oxychloride (20.4 g, 12.2 mL, 133 mmol) was added dropwise allowing the temperature to exceed 10 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h and then it was slowly poured into a mixture of sodium carbonate (55 g) and ice (ca 800 g). After the ice melted, the resulting slurry was filtered and the solid collected was washed with water (2 x 150 mL). The product was dried in vacuo to afford a yellow powder (14.4 g, 97 mmol, 76%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.68 (br. s, 1H), 7.38 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 2.2 Hz, 1H), 6.74 (dd, J = 8.5, 2.2 Hz, 1H), 2.50 (s, 3H).

Step II:

2-Methyl-1,3-benzoxazol-6-yl benzoate

To a stirred suspension of 2-methyl-1,3-benzoxazol-6-ol (2.99 g, 20 mmol) in dichloromethane (50 mL) was added triethylamine (4.05 g, 5.58 mL, 40 mmol). A solution of benzoyl chloride (3.09 g, 2.56 mL, 22 mmol) in dichloromethane (20 mL) was added dropwise over ca. 10 min. The reaction mixture was stirred at room temperature for 2.5 h, then washed with water (2 x 50 mL), and dried over Na_2SO_4, filtered and concentrated in vacuo to give the subtitled compound as a colourless solid (5.05 g, 20 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.22 (m, 2H), 7.66 (m, 2H), 7.53 (m, 2H), 7.40 (d, 1H), 7.16 (dd, 1H), 2.65 (s, 3H).

APCI-MS: m/z 254 [MH^+].

Step III:

4-(Acetylamino)-3-hydroxyphenyl benzoate

To a solution of 2-methyl-1,3-benzoxazol-6-yl benzoate (5.05 g, 20 mmol) in THF (100 mL) a mixture trifluoroacetic acid/water (4 ml/10 mL) was added. The reaction mixture was stirred at room temperature for 16 h, then saurated aqueous $NaHCO_3$ (150 mL) was added. The mixture was extracted with ethyl acetate (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give the subtitled compound.

^{1}H-NMR (400 MHz, acetone-d_6): δ 9.76 (br.s, 1H), 9.32 (br.s, 1H), 8.15 (m, 2H), 7.71 (m, 1H), 7.60 (m, 2H), 7.47 (d, 1H), 6.85 (m, 1H), 6.75 (m, 1H), 2.20 (s, 3H).

APCI-MS: m/z 272 [MH^+].

Step IV:

4-(Acetylamino)-3-{[(2S)-2-methyloxiran-2-yl]methoxy}phenyl benzoate

This compound was prepared from 4-(acetylamino)-3-hydroxyphenyl benzoate (2.71 g, 10 mmol) and [(2*S*)-2-methyloxiran-2-yl]methyl 3-nitrobenzenesulfonate using the standard procedure and 1-methylpyrrolidin-2-one as a solvent. Flash chromatography on silica gel (ethyl acetate/*n*-heptane) afforded the subtitled compound as a colourless solid (1.31g, 3.9 mmol, 39 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.41 (d, 1H), 8.18 (m, 2H), 7.91 (br.s, 1H), 7.63 (m, 1H), 7.50 (m, 2H), 6.83 (m, 1H), 4.15 (d, J = 10.8 Hz, 1H), 4.03 (d, J = 10.8 Hz, 1H), 3.99 (d, J = 10.8 Hz, 1H), 2.92 (d, J = 4.6 Hz, 1H), 2.78 (d, J = 4.6 Hz, 1H), 2.22 (s, 3H), 1.48 (s, 3H).

APCI-MS: m/z 342 [MH^+].

Step V:

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

A solution of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (20.0 mg, 0.09 mmol) and 4-(acetylamino)-3-{[(2*S*)-2-methyloxiran-2-yl]methoxy}phenyl benzoate (30.5 mg, 0.09 mmol) in methanol (2 mL) was refluxed for 3 h. The reaction mixture was cooled to room temperature, and 1 drop of 20 % NaOH in ethanol was added. The mixture was stirred at room temperature for 3 h. The solvent was distilled off under reduced pressure. The residue was purified by HPLC (Kromasil column; eluant: [acetonitrile + 0.1 % trifluoroacetic acid (TFA)/water + 0.1 % TFA]) to afford a colourless solid (41 mg, 0.07 mmol, 79 %).

^{1}H-NMR (400 MHz, acetone-d_6): δ 8.67 (br. s, 1H), 7.71 (d, J = 7.0 Hz, 1H), 7.22 (s, 1H), 7.12 (dd, J = 2.3, 8.5 Hz, 1H), 6.75 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 2.6 Hz, 1H), 6.42 (dd, J = 2.6, 8.6 Hz, 1H), 4.03 (d, 1H), 3.97 (d, J = 9.7 Hz, 1H), 3.92 (br.s, 1H), 3.82 (br. s, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.52 (m, 3H), 2.1 – 2.5 (m, 4H), 2.10 (s, 3H), 1.51 (s, 3H). APCI-MS: m/z 461 [MH^+].

Example 10

***N*-(5-Chloro-2-{[(2S)-3-(6-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

Step I:

***N*-(5-Chloro-2-hydroxyphenyl)acetamide**

To a suspension of 2-amino-4-chlorophenol (1.43 g, 10.0 mmol) in methanol was added acetic anhydride (0.945 mL, 10.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. The volatiles were removed in vacuo to give the subtitled compound (1.5 g).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.20 (br.s, 1H); 9.21 (s, 1H); 8.00 (d, J = 2.6 Hz, 1H); 6.94 (dd, J = 2.6, 8.7 Hz, 1H); 6.84 (d, J = 8.7 Hz, 1H); 2.02 (s, 3H).

Step II:

***N*-{5-Chloro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide**

A mixture of *N*-(5-chloro-2-hydroxyphenyl)acetamide (500 mg, 2.69 mmol), (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (697 mg, 2.69 mmol) and Cs_2CO_3 (1.04 g, 3.22 mmol) in DMF (10 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate in petroleum ether) to give the subtitled compound (600 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.47 (d, J = 2.3 Hz, 1H); 7.93 (br.s, 1H); 6.98 (dd, J = 2.3, 8.7 Hz, 1H); 6.83 (d, J = 8.7 Hz, 1H); 4.36 (dd, J = 2.4, 11.3 Hz, 1H); 3.94 (dd, J = 6.1, 11.3 Hz, 1H); 3.39 (m, 1H); 2.98 (m, 1H); 2.81 (dd, J = 2.7, 4.8 Hz, 1H); 2.22 (s, 3H). APCI-MS: m/z 242 (MH^+).

Step III:

***N*-(5-Chloro-2-{[(2S)-3-(6-chloro-*1'H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (26 mg, 0.116 mmol) and *N*-{5-chloro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (28 mg, 0.116 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (28 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 8.18 (d, J = 2.4 Hz, 1H); 7.30-7.20 (m,. 3H); 7.10-7.00 (m, 2H); 5.02 (s, 2H); 4.23 (m, 1H); 4.14 (dd, J = 3.1, 9.9 Hz, 1H); 3.99 (dd, J = 6.5, 9.9 Hz, 1H); 2.93 (m, 2H); 2.63 (d, J = 6.3 Hz, 2H); 2.55 (m, 2H); 2.21 (s, 3H); 2.00 (m, 2H); 1.73 (m, 2H).

APCI-MS: m/z 467 (MH^+).

Example 11

***N*-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide**

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (30 mg, 0.134 mmol) and *N*-{4-fluoro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (30 mg, 0.134 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (40 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.90 (dd, J = 6.2, 8.9 Hz, 1H); 7.29-7.20 (m, 3H); 6.89 (dd, J = 2.7, 10.5 Hz, 1H); 6.67 (m, 1H); 5.02 (s, 2H); 4.23 (m, 1H); 4.13 (dd, J = 3.1, 9.9 Hz, 1H); 4.01 (dd, J = 6.3, 9.9 Hz, 1H); 2.93 (m, 2H); 2.69-2.50 (m, 4H); 2.20 (s, 3H); 2.00 (m, 2H); 1.73 (br.d, J = 13.5 Hz, 2H).
APCI-MS: m/z 451(MH^+).

Example 12

***N*-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (25 mg, 0.111 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (23 mg, 0.111 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (20 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 8.00 (dd, J = 1.3, 8.0 Hz, 1H); 7.30-7.20 (m, 3H); 7.12-7.05 (m, 2H); 6.93 (m, 1H); 5.01 (s, 2H); 4.22 (m, 1H); 4.14 (dd, J = 3.3, 9.9 Hz, 1H); 4.00

(dd, J = 6.4, 9.9 Hz, 1H); 2.94 (m, 2H); 2.69-2.52 (m, 4H); 2.20 (s, 3H); 2.01 (m, 2H); 1.74 (br.d, J = 13.5 Hz, 2H).
APCI-MS: m/z 433(MH^+).

Example 13

***N*-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide**

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (46 mg, 0.205 mmol) and *N*-{4-methoxy-2[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (48.6 mg, 0.205 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (80 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.75 (d, J = 8.9 Hz, 1H); 7.29-7.20 (m, 3H); 6.64 (d, J = 2.7 Hz, 1H); 6.51 (dd, J = 2.7, 8.9 Hz, 1H); 5.02 (s, 2H); 4.44 (m, 1H); 4.12 (dd, J = 3.3, 10.0 Hz, 1H); 3.98 (dd, J = 6.2, 10.0 Hz, 1H); 3.80 (s, 3H); 2.96 (m, 2H); 2.68-2.50 (m, 4H); 2.18 (s, 3H); 2.00 (m, 2H); 1.74 (br.d, J = 13.2 Hz, 2H).
APCI-MS: m/z 461(MH^+).

Example 14

2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide

A mixture of 6-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (25 mg, 0.111 mmol) and *N*-cyclopropyl-4-fluoro-2-(oxiran-2-ylmethoxy)benzamide (28 mg, 0.111 mmol) in ethanol was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (32 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.98 (dd, J = 6.9, 8.8 Hz, 1H); 7.29-7.20 (m, 3H); 6.98 (dd, J = 2.4, 10.8 Hz, 1H); 6.82 (ddd, J = 2.4, 8.0, 8.8 Hz, 1H); 5.01 (s, 2H); 4.25 (dd, J = 3.1, 9.4 Hz, 1H); 4.19 (m, 1H); 4.11 (dd, J = 5.5, 9.4 Hz, 1H); 2.92 (m, 3H); 2.59 (m, 4H); 2.01 (m, 2H); 1.73 (m, 2H); 0.80 (m, 2H); 0.69 (m, 2H).

APCI-MS: m/z 477(MH^+).

Example 15

***N*-(2{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]phenyl)acetamide**

A mixture of 5-fluoro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (15 mg, 0.072 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (15 mg, 0.072 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (9 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.99 (dd, J = 1.2, 8.0 Hz, 1H); 7.18 (dd, J = 4.9, 8.0 Hz, 1H); 7.11-6.90 (m, 5H); 5.00 (s, 2H); 4.27 (m, 1H); 4.13 (dd, J = 3.2, 9.9 Hz, 1H); 3.99 (dd, J = 6.4, 9.9 Hz, 1H); 2.99 (m, 2H); 2.72-2.52 (m, 4H); 2.20 (s, 3H); 2.02 (m, 2H); 1.73 (br.d, J = 13.6 Hz, 2H).

APCI-MS: m/z 415(MH^+).

Example 16

***N*-(4-Chloro-2-{[(2S)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

Step I:

***N*-(4-Chloro-2-hydroxyphenyl)acetamide**

To a suspension of 2-amino-5-chlorophenol (1.01g, 7.0 mmol) in methanol (10 mL) was added acetic anhydride (1.08 g, 10.55 mmol) and the reaction mixture was stirred at room

temperature for 30 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (hexane:ethyl acetate 5:2) to give the subtitled compound (1.19 g).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 10.29 (br.s, 1H); 9.26 (br.s, 1H); 7.77 (d, J = 8.6 Hz, 1H); 6.86 (d, J = 2.4 Hz, 1H); 6.80 (dd, J = 2.4, 8.6 Hz, 1H); 2.12 (s, 3H).
APCI-MS: m/z 186(MH^+).

Step II:

***N*-{4-Chloro-2-[(2S)-oxiran-2ylmethoxy]phenyl}acetamide**

To a mixture of (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (3.37 g, 13.25 mmol), N-(4-chloro-2-hydroxyphenyl)acetamide (2.46g, 17.23 mmol) and Cs_2CO_3 (6.48g, 19.88 mmol) was added DMF (20 mL) at 0 ^{0}C and the reaction mixture was stirred at 0 ^{0}C for 3h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (hexane:ethyl acetate 3:2) to give the subtitled compound (2.36 g).

^{1}H-NMR (CD_3COCD_3, 400 MHz): δ 8.67 (br.s, 1H); 8.30 (d, J = 8.7 Hz, 1H); 7.07 (d, J = 2.3 Hz, 1H); 6.95 (dd, J = 2.2, 8.7 Hz, 1H); 4.46 (dd, J = 2.3, 11.5 Hz, 1H); 3.94 (dd, J = 6.6, 11.5 Hz, 1H); 3.34 (m, 1H); 2.87 (dd, J = 4.3, 5.0 Hz, 1H); 2.73 (dd, J = 2.7, 5.0 Hz, 1H); 2.18 (s, 3H).

Step III

***N*-(4-Chloro-2-{[(2S)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

A mixture of 3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one (Marxer, A; Rodriguez, H. R; McKenna, J. M; Tsai, H. M., *J. Org. Chem.*, **1975**, *40*, 1427-1433) (61 mg, 0.3 mmol) and *N*-{4-chloro-2-[(2S)-oxiran-2ylmethoxy]phenyl}acetamide (72.5 mg, 0.3 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the

residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (40 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.93 (d, J = 7.7 Hz, 1H); 7.84 (m, 2H); 7.71-7.61 (m, 2H); 7.13 (d, J = 2.0 Hz, 1H); 7.00 (dd, J = 2.0, 8.5 Hz, 1H); 4.58 (m, 1H); 4.13 (m, 2H); 3.86 (m, 2H); 3.65-3.45 (m, 4H); 2.64 (m, 2H); 2.20 (s, 3H); 2.06 (m, 2H).
APCI-MS: m/z 445(MH^+).

Example 17

***N*-Cyclopropyl-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}benzamide**

A mixture 3*H*-spiro[2-benzofuran-1,4'-piperidine] (Marxer, A; Rodriguez, H. R; McKenna, J. M; Tsai, H. M., *J. Org. Chem.*, **1975**, *40*, 1427-1433) (46.5 mg, 0.246 mmol) and *N*-cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (57.4 mg, 0.246 mmol) in ethanol (3 mL) was kept on stirring at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (55 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.43 (d, J = 1.8 Hz, 1H); 8.20 (dd, J = 1.8, 7.8 Hz, 1H); 7.40 (m, 1H); 7.30 (m, 2H); 7.23 (m, 1H); 7.18 (m, 1H); 7.08 (t, J = 7.5 Hz, 1H); 6.93 (d, J = 8.2 Hz, 1H); 5.10 (s, 2H); 4.20 (m, 2H); 4.00 (dd, J = 5.0, 9.3 Hz, 1H); 3.02 (m, 2H); 2.85 (m, 2H); 2.69 (m, 1H); 2.58 (m, 2H); 2.02 (m, 2H); 1.82 (d, 2H); 0.85 (m, 2H); 0.63 (m, 2H).
APCI-MS: m/z 423(MH^+).

Example 18

***N*-(4-Chloro-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

A mixture 3*H*-spiro[2-benzofuran-1,4'-piperidine] (38 mg, 0.2 mmol) and *N*-{4-chloro-2-[(2S)-oxiran-2ylmethoxy]phenyl}acetamide (48.3 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (35 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.7 Hz, 1H); 7.29-7.18 (m, 4H); 7.10 (d, *J* = 2.2 Hz, 1H); 6.94 (dd, *J* = 2.2, 8.7 Hz, 1H); 5.08 (s, 2H); 4.26 (m, 1H); 4.16 (dd, *J* = 3.0, 10.0 Hz, 1H); 4.01 (dd, *J* = 6.4, 9.9 Hz, 1H); 2.97 (m, 2H); 2.69-2.52 (m, 4H); 2.19 (s, 3H); 2.07 (m, 2H); 1.73 (m, 2H).
APCI-MS: m/z 433(MH^+).

Example 19

***N*-(5-Chloro-2{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

A mixture 3*H*-spiro[2-benzofuran-1,4'-piperidine] (63 mg, 0.33 mmol) and *N*-{5-chloro-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (80 mg, 0.33 mmol) in ethanol (5 mL) was stirred at 77 ^{0}C for 4h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in chloroform) to give the titled compound (77 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.50 (m, 1H); 7.31 (m, 3H); 7.18 (m, 1H); 6.98 (m, 1H); 6.83 (m, 1H); 5.10 (s, 2H); 4.10 (m, 1H); 4.03 (dd, 1H); 3.91 (dd, 1H); 2.97 (m, 1H); 2.76 (m, 2H); 2.60-2.43 (m, 3H); 2.20 (s, 3H); 2.05-1.89 (m, 2H); 1.60 (m, 2H).
APCI-MS: m/z 431(MH^+).

Example 20

***N*-(2-{[(2S)-2-hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide**

Step I:

[(2S)-2-Methyloxiranyl]methyl3-nitrobenzenesulfonate

To an oven-dried 1000 mL three-necked flask was added powdered activated molecular sieves (8.0 g, 4Å) and CH_2Cl_2 (440 mL), D-(-)-diisopropyl tartrate (4 mL, 14.2 mmol) and 2-methyl-2-propene-1-ol (20 mL, 240 mmol) was added and the mixture was cooled to -20 ^{0}C. Titanium tetraisopropoxide (3.5 mL, 11.9 mmol) was added with a few mL of CH_2Cl_2 and the mixture was stirred at –20 ^{0}C for 30 min. Cumene hydroperoxide (75 mL, 430 mmol) was added dropwise over 1.5 hours maintaining the temperature at –20 ^{0}C. The mixture was stirred at this temperature overnight. Trimethyl phosphite (40 mL, 340 mmol) was added dropwise over 5 hours maintaining the temperature at –20 ^{0}C. Triethylamine (50 mL, 360 mmol) and 4-dimethylaminopyridine (DMAP) (3.48 g, 28.5 mmol) was added followed by a solution of 3-nitrobenzenesulphonyl chloride (47 g, 212 mmol) in CH_2Cl_2 (400 mL). The temperature was raised to –10 ^{0}C and the mixture was stirred at this temperature overnight. After removing the external cooling vessel, the reaction mixture was filtered through celite. The organic phase was washed with 10% tartaric acid (500 mL), saturated $NaHCO_3$ (300 mL) and brine (300 mL). The organic layer was dried over magnesium sulphate ($MgSO_4$) and concentrated in vacuo to give 150 g of a yellow oil. The crude material was purified by silica gel flash chromatography (0-50% ethyl acetate in heptane) to give the subtitled compound (48.8 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.79-8.75 (m, 1H); 8.52 (ddd, J = 1.1, 2.3, 8.3 Hz, 1H); 8.25 (ddd, J = 1.1, 1.8, 7.8 Hz, 1H); 7.81 (t, J = 8.5 Hz, 1H); 4.28 (d, J = 11.3 Hz, 1H); 4.05 (d, J = 11.3 Hz, 1H); 2.73 (d, J = 4.4 Hz, 1H); 2.67 (d, J = 4.4 Hz, 1H); 1.56 (s, 3H).

Step II:

***N*-(4-Methoxy-2-{[(2S)-2-methyloxiran-2-yl]methoxy}phenyl)acetamide**

A mixture of [(2S)-2-methyloxiran-2-yl]methyl3-nitrobenzenesulfonate (2.04 g, 7.46 mmol), *N*-(2-hydroxy-4-methoxyphenyl)acetamide ((1.04 g, 5.74 mmol) and Cs_2CO_3 (2.80 g, 8.61 mmol) in DMF (12 mL) was kept on stirring at room temperature overnight.

The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (ethyl acetate : hexane 1:1) to give the subtitled compound (1.19 g).

^{1}H-NMR ($CDCl_3$, 400MHz): δ 8.20 (d, J = 8.8 Hz, 1H); 7.72 (br.s, 1H); 6.52 (m, 2H); 4.12 (d, J = 11.0 Hz, 1H); 3.98 (d, J = 11.0 Hz, 1H); 3.77 (s, 3H); 2.91 (d, J = 4.7 Hz, 1H); 2.77 (d, J = 4.7 Hz, 1H); 2.20 (s, 3H); 1.48 (s, 3H).

Step III:

***N*-(2-{[(2S)-2-Hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide**

A mixture of 3*H*-spiro[2-benzofuran-1,4'-piperidine] (57 mg, 0.3 mmol) and *N*-(4-methoxy-2-{[(2S)-2-methyloxiran-2-yl]methoxy}phenyl)acetamide (75.4 mg, 0.3 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (70 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.65 (d, J = 8.8 Hz, 1H); 7.28-7.15 (m, 4H); 6.61 (d, J = 2.7 Hz, 1H); 6.50 (dd, J = 2.7, 8.8 Hz, 1H); 5.10 (s, 2H); 3.99 (d, J = 9.2 Hz, 1H); 3.90 (d, J = 9.2 Hz, 1H); 3.79 (s, 3H); 2.88 (m, 2H); 2.73-2.53 (m, 4H); 2.16 (s, 3H); 2.00 (m, 2H); 1.63 (m, 2H); 1.31 (s, 3H).

APCI-MS: m/z 441(MH^+).

Example 21

***N*-[2-{[(2S)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-5-(trifluoromethyl)phenyl]acetamide**

Step I:

***N*-[2-[(2S)-Oxiran-2-ylmethoxy]-5-(trifluoromethyl)phenyl]acetamide**

A mixture of *N*-[2-hydroxy-5-(trifluoromethyl)phenyl]acetamide (282 mg, 1.28 mmol), (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (331.5 mg, 1.28 mmol) and Cs_2CO_3 (487.5 mg, 1.28 mmol) in DMF (5 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (150 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.72 (br.s, 1H); 7.90 (br.s, 1H); 7.31 (m, 1H); 6.97 (d, 1H); 4.46 (dd, J = 2.4, 11.3 Hz, 1H); 4.00 (dd, J = 6.3, 11.3 Hz, 1H); 3.44 (m, 1H); 3.00 (d, J = 4.5 Hz, 1H); 2.80 (dd, J = 2.7, 4.8 Hz, 1H); 2.25 (s, 3H).

Step II:

***N*-[2-{[(2S)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-5-(trifluoromethyl)phenyl]acetamide**

A mixture of 3*H*-spiro[2-benzofuran-1,4'-piperidine] (47.3 mg, 0.25 mmol) and *N*-[2-[(2S)-oxiran-2-ylmethoxy]-5-(trifluoromethyl)phenyl]acetamide (69 mg, 0.25 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (38 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 8.49 (d, 1H); 7.39 (dd, 1H); 7.30-7.17 (m, 5H); 5.08 (s, 2H); 4.28 (m, 2H); 4.10 (dd, J = 6.5, 9.8 Hz, 1H); 2.98 (m, 2H); 2.68-2.53 (m, 4H); 2.22 (s, 3H); 2.02 (m, 2H); 1.73 (m, 2H).

APCI-MS: m/z 465(MH^+).

Example 22

***N*-(2-{[(2S)-2-Hydroxy-3-(2-methyl-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

A mixture of 2-methylspiro[indene-1,4'-piperidine] (Efange, S. M. N; Khare, A. B; Foulon, C; Akella, S. K; Parsons, S. M., *J. Med. Chem.*, **1994**, *37*, 2574-2582) (82.5 mg, 0.35 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (72.5 mg, 0.35 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (80 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.84 (m, 2H); 7.28 (m, 2H); 7.16 (m, 2H); 7.07 (m, 1H); 6.98 (m, 1H); 6.53 (br.s, 1H); 4.58 (m, 1H); 4.14 (m, 2H); 3.90-3.49 (m, 6H); 2.45 (m, 2H); 2.19 (s, 3H); 1.99 (s, 3H); 1.40 (br.t, J = 14.0 Hz, 2H).
APCI-MS: m/z 407(MH^+).

Example 23

***N*-(2-{[(2S)-3-(2,3-Dihydro-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 2,3-dihydrospiro[indene-1,4'-piperidine] (Efange, S. M. N; Khare, A. B; Foulon, C; Akella, S. K; Parsons, S. M., *J. Med. Chem.*, **1994**, *37*, 2574-2582; Chambers, M. S; Baker, R; Billington, D. C; Knight, A. K; Middlemiss, D. N; Wong, E. H. F., *J. Med. Chem.*, **1992**, *35*, 2033-2039). (78.3 mg, 0.35 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (72.5 mg, 0.35 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% NH_4OH) to give the titled compound (65 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.82 (m, 1H); 7.26-7.12 (m, 5H); 7.06 (m, 1H); 6.98 (m, 1H); 4.50 (m, 1H); 4.10 (d, 2H); 3.72 (m, 2H); 3.45-3.22 (m, 5H); 2.99 (t, J = 7.3 Hz, 2H); 2.33-2.13 (m, 6H); 1.82 (m, 2H).
APCI-MS: m/z 395(MH^+).

Example 24

***N*-(2-{[(2S)-2-Hydroxy-3-(2-oxo-1'*H*-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide**

A mixture of spiro[1-benzofuran-3,4'-piperidin]-2-one (80 mg, 0.28 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (60 mg, 0.28 mmol) in ethanol (2 mL) was kept on stirring at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by high pressure liquid chromatography (HPLC) to give the titled compound (65 mg).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 9.03 (br.s, 1H); 7.95-7.90 (m, 1H); 7.44-7.39 (m, 1H); 7.32-7.24 (m, 3H); 7.05 (m, 2H); 6.94 (m, 1H); 6.09 (br.s, 1H); 4.41 (m, 1H); 4.07-3.91 (m, 2H); 3.74-3.36 (m, 8H); 2.31-2.22 (m, 2H); 2.11 (s, 3H).
APCI-MS: m/z 411(MH^+).

Example 25

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

Step I:

Methyl 2-hydroxy-4-(trityloxy)benzoate

To a solution of methyl 2,4-dihydroxybenzoate (388 mg, 2.0 mmol) in dimethylformamide (5 mL) was added triethylamine, Et_3N, (0.556 mL, 4.0 mmol) followed by trityl chloride (557.5 mg, 2.0 mmol) and 4-dimethylaminopyridine (DMAP) (20 mg). The reaction mixture was kept on stirring at room temperature overnight, poured into a mixture of ice-water, the white precipitate was collected by filtration. This precipitate was subjected to silica gel flash chromatography (0-5% ethyl acetate in petroleum ether) to give the subtitled compound (350 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 10.65 (s, 1H); 7.58-7.22 (m, 16H); 6.38 (m, 2H); 3.89 (s, 3H).

Step II:

***N*-Cyclopropyl-2-hydroxy-4-(trityloxy)benzamide**

Methyl 2-hydroxy-4-(trityloxy)benzoate (340 mg, 0.83 mmol) was dissolved in cyclopropylamine (3 mL) and left at room temperature for a week. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-20% ethyl acetate in petroleum ether) to give the subtitled compound (210 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 12.30 (s, 1H); 7.48 (m, 6H); 7.35-7.22 (m, 9H); 6.92 (d, J = 9.0 Hz, 1H); 6.31 (d, J = 2.4 Hz, 1H); 6.24 (dd, J = 2.4, 8.8 Hz, 1H); 6.08 (br. S, 1H); 2.80 (m, 1H); 0.85 (m, 2H); 0.60 (m, 2H).

Step III:

***N*-Cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]-4-(trityloxy)benzamide**

A mixture of (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (119 mg, 0.459 mmol), *N*-cyclopropyl-2-hydroxy-4-(trityloxy)benzamide (200 mg, 0.459 mmol) and cesium carbonate, Cs_2CO_3, (186.2 mg, 0.573 mmol) in dimethylformamide (3 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4, filtered, concentrated and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (160 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.04 (s, 1H); 7.86 (d, J = 8.8 Hz, 1H); 7.73 (br.d, J = 3.0 Hz, 1H); 7.46-7.39 (m, 5H); 7.34-7.23 (m, 9H); 6.44 (dd, J = 2.2, 8.8 Hz, 1H); 6.23 (d, J = 2.2 Hz, 1H); 4.03 (dd, J = 2.7, 10.8 Hz, 1H); 3.68 (dd, J = 5.0, 10.8 Hz, 1H); 3.23 (m, 1H); 2.88 (m, 2H); 2.70 (dd, J = 2.7, 4.9 Hz, 1H); 0.80 (m, 2H); 0.58 (m, 2H).

Step IV:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

A mixture of *N*-cyclopropyl-2-[(2S)-oxiran-2-ylmethoxy]-4-(trityloxy)benzamide (152 mg, 0.307 mmol) and 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (69 mg, 0.307 mmol) in ethanol (3 mL) was kept on stirring at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was treated with 80% aqueous acetic acid (10 mL) at reflux for 90 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2%NH_4OH) to give the titled compound (75 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.83 (d, J = 8.4 Hz, 1H); 7.13 (m, 1H); 6.94 (dd, J = 2.3, 8.4 Hz, 1H); 6.65 (d, J = 8.4 Hz, 1H); 6.51-6.45 (m, 2H); 4.21-4.13 (m, 2H); 4.08-4.02 (m, 1H); 3.01 (s, 2H); 2.90 (m, 1H); 2.75 (br.s, 4H); 2.58 (d, J = 6.2 Hz, 2H); 1.98 (m, 2H); 1.88 (m, 2H); 0.80 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 473(MH^+).

Example 26

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

Step I:

***N*-Cyclopropyl-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzamide**

Methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (Percec, V; Tomazos, D. *J. Mater. Chem.* 1993, *3*, 643-650) (530 mg, 1.83 mmol) was dissolved in cyclopropyl amine (3 mL) and left at room temperature for a week. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (407 mg).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 13.20 (br.s, 1H); 8.56 (d, J = 2.7 Hz, 1H); 7.72 (d, J = 8.7 Hz, 1H); 7.38-7.33 (m, 2H); 6.96-6.92 (m, 2H); 6.49-6.45 (m, 2H); 5.00 (s, 2H); 3.79 (s, 3H); 2.80 (m, 1H); 0.78 (m, 2H); 0.58 (m, 2H).

Step II:

[(2S)-2-Methyloxiranyl]methyl3-nitrobenzenesulfonate

To an oven-dried 1000 mL three-necked flask was added powdered activated molecular sieves (8.0 g, 4Å) and dichloromethane, CH_2Cl_2, (440 mL), D-(-)-diisopropyl tartrate (4 mL, 14.2 mmol) and 2-methyl-2-propene-1-ol (20 mL, 240 mmol) was added and the mixture was cooled to –20 ^{0}C. Titanium tetraisopropoxide (3.5 mL, 11.9 mmol) was added with a few mL of dichloromethane and the mixture was stirred at –20 ^{0}C for 30 min. Cumene hydroperoxide (75 mL, 430 mmol) was added dropwise over 1.5 hours maintaining the temperature at –20 ^{0}C. The mixture was stirred at this temperature overnight. Trimethyl phosphite (40 mL, 340 mmol) was added dropwise over 5 hours maintaining the temperature at –20 ^{0}C. Triethyl amine (50 mL, 360 mmol) and 4-dimethylaminopyridine (DMAP) (3.48 g, 28.5 mmol) was added followed by a solution of 3-nitrobenzenesulphonyl chloride (47 g, 212 mmol) in dichloromethane (400 mL). The temperature was raised to –10 ^{0}C and the mixture was stirred at this temperature overnight. After removing the external cooling vessel, the reaction mixture was filtered through celite. The organic phase was washed with 10% tartaric acid (500 mL), saturated sodium hydrogencarbonate, $NaHCO_3$, (300 mL) and brine (300 mL). The organic layer was dried over magnesium sulphate, $MgSO_4$, and concentrated in vacuo to give 150 g of a yellow oil. The crude material was purified by silica gel flash chromatography (0-50% ethyl acetate in heptane) to give the subtitled compound (48.8 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.79-8.75 (m, 1H); 8.52 (ddd, J = 1.1, 2.3, 8.3 Hz, 1H); 8.25 (ddd, J = 1.1, 1.8, 7.8 Hz, 1H); 7.81 (t, J = 8.5 Hz, 1H); 4.28 (d, J = 11.3 Hz, 1H); 4.05 (d, J = 11.3 Hz, 1H); 2.73 (d, J = 4.4 Hz, 1H); 2.67 (d, J = 4.4 Hz, 1H); 1.56 (s, 3H).

Step III:

***N*-Cyclopropyl-4-[(4-methoxybenzyl)0xy]-2-{[(2S)-2-methloxiran-2-yl]methoxy}benzamide**

A mixture of [(2S)-2-methyloxiran-2-yl]methyl3-nitrobenzenesulfonate (218 mg, 0.797 mmol), *N*-cyclopropyl-2-hydroxy-4-[(4-methoxybenzyl)oxy]benzamide (250 mg, 0.797 mmol) and cesium carbonate, Cs_2CO_3, (311 mg, 0.956 mmol) in dimethylformamide (5 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4, filtered, concentrated and the residue was purified by silica gel flash chromatography (0-40% ethyl acetate in petroleum ether) to give the subtitled compound (260 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.19 (d, J = 8.8 Hz, 1H); 7.90 (d, J = 3.0 Hz, 1H); 7.38-7.33 (m, 2H); 6.96-6.92 (m, 2H); 6.70 (dd, J = 2.3, 8.8 Hz, 1H); 6.48 (d, J = 2.3 Hz, 1H); 5.02 (s, 2H); 4.14 (d, J = 10.3 Hz, 1H); 4.06 (d, J = 10.3 Hz, 1H); 3.80 (s, 3H); 3.04-2.98 (m, 1H); 2.94 (d, J = 4.7 Hz, 1H); 2.87 (d, J = 4.7 Hz, 1H); 1.50 (s, 3H); 0.86 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 384(MH^+).

Step IV:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (70 mg, 0.313 mmol) and *N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]-2-{[(2S)-2-methloxiran-2-yl] methoxy}benzamide (120 mg, 0.313 mmol) in ethanol (3 mL) was kept on stirring at 80 ^{0}C for 6h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (100 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.22-8.15 (m, 2H); 7.39-7.34 (m, 2H); 7.13-7.06 (m, 2H); 6.97-6.92 (m, 2H); 6.72-6.66 (m, 2H); 6.50 (d, J = 2.3 Hz, 1H); 5.08 (s, 2H); 3.88 (s, 3H); 3.05 (m, 1H); 2.99 (s, 2H); 2.90 (m, 2H); 2.75 (m, 1H); 2.66 (d, J = 13.8 Hz, 1H); 2.64 (m, 1H); 2.49 (d, J = 13.8 Hz, 1H); 1.99 (m, 2H); 1.82 (m, 2H); 1.60 (br.s, 2H); 1.33 (s, 3H); 0.86 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 607(MH^+).

Step V:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide (80 mg, 0.131 mmol) was treated with 10% trifluoroacetic acid in dichloromethane (10 mL) at room temperature for 15 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (40 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.83 (m, 1H); 7.12 (m, 1H); 7.03 (dd, J = 2.3, 8.5 Hz, 1H); 6.64 (d, J = 8.5 Hz, 1H); 6.49-6.45 (m, 2H); 4.09 (d, J = 9.2 Hz, 1H); 3.90 (d, J = 9.2 Hz, 1H); 2.99 (s, 2H); 2.92 (m, 1H); 2.79 (m, 2H); 2.66 (m, 2H); 2.58 (d, J = 13.9 Hz, 1H); 2.50 (d, J = 13.9 Hz, 1H); 1.93-1.75 (m, 4H); 1.31 (s, 3H); .80 (m, 2H); 0.68 (m, 2H).

APCI-MS: m/z 487(MH^+).

Example 27

2-{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-methylbenzamide

Step I:

2-Hydroxy-*N*-methylbenzamide

A solution of methyl salicylate (5.16 mL, 40 mmol) in methanol (10 mL) was added dropwise to aqueous 40% methylamine (18.1 mL, 210 mmol) at 0 °C. After addition was complete the reaction mixture was kept on stirring at room temperature overnight. The volatiles were removed in vacuo to give the subtitled compound (5.48 g).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.70 (dd, J = 1.5, 7.9 Hz, 1H); 7.38-7.32 (, 2H); 6.90-6.83 (m, 2H); 2.85 (s, 3H).

Step II:

***N*-Methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide**

A mixture of (2S)-oxiran-2-ylmethyl-3-nitrobenzenesulfonate (388.5 mg, 1.50 mmol), 2-hydroxy-*N*-methylbenzamide (226.5 mg, 1.50 mmol) and cesium carbonate, Cs_2CO_3, (586 mg, 1.80 mmol) in dimethylformamide (6 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was dried over sodium sulphate, Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-50% ethyl acetate in petroleum ether) to give the subtitled compound (284 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.39 (m, 1H); 7.90 (br.s, 1H); 7.06-6.98 (m, 2H); 6.95-6.89 (m, 1H); 4.38 (dd, *J* = 2.5, 11.4 Hz, 1H); 3.98 (dd, *J* = 6.0, 11.4 Hz, 1H); 3.40 (m, 1H); 2.97 (t, *J* = 5.0 Hz, 1H); 2.81 (dd, *J* = 2.7, 4.8 Hz, 1H); 2.21 (s, 3H).
APCI-MS: m/z 208(MH^+).

Step III:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (40 mg, 0.178 mmol) and *N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (37 mg, 0.178 mmol) in ethanol (2 mL) was kept on stirring at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in

dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (46 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.99 (dd, J = 1.4, 8.0 Hz, 1H); 7.14 (m, 1H); 7.11-7.00 (m, 3H); 6.92 (m, 1H); 6.65 (d, J = 8.5 Hz, 1H); 4.20 (m, 1H); 4.13 (dd, J = 3.2, 9.9 Hz, 1H); 3.98 (dd, J = 6.3, 9.9 Hz, 1H); 3.01 (s, 2H); 2.76-2.65 (br.s, 4H); 2.62 (dd, J = 1.4, 5.4 Hz, 2H); 2.18 (s, 3H); 1.98-1.92 (m, 2H); 1.89-1.79 (m, 2H).
APCI-MS: m/z 487(MH^+).

Example 28

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxy-*N*-methylbenzamide (trifluoroacetate)

Step I:

2-Hydroxy-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

To a suspension of methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (500 mg, 1.73 mmol) in methanol (15 mL) was slowly added aqueous 40% methylamine (3 mL) at 0 ^{0}C. After addition was complete the reaction mixture was kept on stirring at room temperature for 2 days. The volatiles were removed in vacuo to give the subtitled compound (500 mg).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 13.20 (br.s, 1H); 8.60 (m, 1H); 7.70 (d, J = 8.8 Hz, 1H); 7.35 (m, 2H); 6.96-6.92 (m, 2H); 6.50 (dd, J = 2.6, 8.8 Hz, 1H); 6.42 (d, J = 2.6 Hz, 1H)5.04 (s, 2H); 3.76 (s, 3H); 2.79 d, J = 4.6 Hz, 3H).
APCI-MS: m/z 288(MH^+).

Step II:

4-[(4-Methoxybenzyl)oxy]-*N*-methyl-2-{[(2S)-2-methyloxiran-2-yl]methoxy}benzamide

A mixture of [(2S)-2-methyloxiran-2-yl]methyl3-nitrobenzenesulfonate (133 mg, 0.487 mmol), 2-hydroxy-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (140 mg, 0.487 mmol)

and cesium carbonate, Cs_2CO_3, (198 mg, 0.608 mmol) in dimethylformamide (5 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-60% ethyl acetate in petroleum ether) to give the subtitled compound (130 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, J = 8.8 Hz, 1H); 7.82 (m, 1H); 7.37 (m, 2H); 6.97-6.92 (m, 2H); 6.71 (dd J = 2.3, 8.8 Hz, 1H); 6.53 (d, J = 2.3 Hz, 1H); 5.01 (s, 2H); 4.18 (d, J = 10.5 Hz, 1H); 4.10 (d, J = 10.5 Hz, 1H); 3.85 (s, 3H); 3.02 (d, J = 4.9 Hz, 3H); 2.97 (d, J = 4.6 Hz, 1H); 2.80 (d, J = 4.6 Hz, 1H); 1.50 (s, 3H).
APCI-MS: m/z 358(MH^+).

Step III:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (70 mg, 0.313 mmol) and 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-{[(2S)-2-methyloxiran-2-yl]methoxy}benzamide (112 mg, 0.313 mmol) in ethanol (2 mL) was kept on stirring at 80 ^{0}C for 4.5 h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (135 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, J = 8.7 Hz, 1H); 8.12 (m, 1H); 7.39-7.35 (m, 2H); 7.12 (m, 2H); 7.08 (dd, J = 2.3, 8.5 Hz, 1H); 6.97-6.92 (m, 2H); 6.72-6.66 (m, 2H); 6.52 (d, J = 2.3 Hz, 1H); 5.05 (s, 2H); 3.90 (m, 2H); 3.82 (s, 3H); 3.0 (d, J = 4.9 Hz, 3H); 2.98 (s, 2H); 2.94-2.84 (m, 2H); 2.73 (m, 1H); 2.69 (d, J = 13.9 Hz, 1H); 2.63 (m, 1H); 2.49 (d, J = 13.9 Hz, 1H); 1.99 (m, 2H); 1.82 (m, 2H).
APCI-MS: m/z 581(MH^+).

Step IV:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxy-*N*-methylbenzamide (trifluoroacetate)

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (125 mg, 0.215 mmol) was treated with 10% trifluoroacetic acid in dichloromethane (10 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified by HPLC (acetonitrile/water (CH_3CN/H_2O), 0.1% trifluoroacetic acid) to give the titled compound (50 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.52-7.47 (m, 1H); 7.20 /br.s, 1H); 7.10 (dd, J = 2.3, 8.5 Hz, 1H); 6.75 (d, J = 8.5 Hz, 1H); 6.52 (br.s, 1H); 6.49 (dd, J = 2.1, 8.5 Hz, 1H); 4.20 (m, 2H); 4.00 (m, 1H); 3.62-3.35 (m, 4H); 3.18 (2xs, 2H); 3.90 (2xs, 3H); 2.60 (m, 2H); 2.32-2.05 (m, 3H); 1.39 (s, 3H).

APCI-MS: m/z 461(MH^+).

Example 29

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy]oxy}-4-hydroxy-*N*-methylbenzamide

Step I:

4-[4-Methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide

A mixture of (2S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (151 mg, 0.584 mmol), methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (168 mg, 0.584 mmol) and cesium carbonate, Cs_2CO_3, (228 mg, 0.70 mmol) in dimethylformamide (4 mL) was kept on stirring at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-90% ethyl acetate in petroleum ether) to give the subtitled compound (150 mg).

^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.90 (m, 1H); 7.75 (d, *J* = 8.7 Hz, 1H); 7.37 (d, *J* = 8.6 Hz, 2H); 6.96-6.91 (m, 2H); 6.74 (d, *J* = 2.3 Hz, 1H); 6.68 (dd, *J* = 2.3, 8.7 Hz, 1H); 5.08 (s, 2H); 4.48 (dd, *J* = 2.5, 11.5 Hz, 1H); 4.04 (dd, *J* = 6.0, 11.5 Hz, 1H); 3.78 (s, 3H); 3.45 (m, 1H); 2.86 (t, *J* = 4.9 Hz, 1H); 2.79 (d, *J* = 4.7 Hz, 3H); 2.73 (dd, *J* = 2.7, 5.0 Hz, 1H).
APCI-MS: m/z 344(MH^+).

Step II:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (70 mg, 0.313 mmol) and 4-[4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (107.5 mg, 0.313 mmol) in ethanol (3 mL) was kept on stirring at 80 ^{0}C for 6h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (122 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, *J* = 8.8 Hz, 1H); 8.10 (m, 1H); 7.34 (d, *J* = 8.7 Hz, 2H); 7.14 (br.s, 1H); 7.08 (m, 1H); 6.95 (d, *J* = 8.7 Hz, 2H); 6.70 (m, 2H); 6.55 (d, *J* = 2.1 Hz, 1H); 5.08 (s, 2H); 4.22-4.12 (m, 2H); 3.98 (dd, *J* = 5.3, 9.3 Hz, 1H); 3.85 (s, 3H); 3.01 (s, 2H); 3.00 (d, *J* = 4.8 Hz, 3H); 2.95-2.87 (m, 1H); 2.80 (m, 1H); 2.65-2.50 (m, 4H); 2.01 (m, 2H); 1.82 (m, 2H).
APCI-MS: m/z 567(MH^+).

Step III:

2-{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy]oxy}-4-hydroxy-N-methylbenzamide

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (110 mg, 0.194 mmol) was treated with 10% trifluoroacetic acid in dichloromethane (10 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified

by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (45 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.81 (d, J = 8.7 Hz, 1H); 7.13 (m, 1H); 7.04 (dd, J = 2.3, 8.5 Hz, 1H); 6.66 (d, J = 8.5 Hz, 1H); 6.52 (d, J = 2.2 Hz, 1H); 6.48 (dd, J = 2.2, 8.6 Hz, 1H); 4.25-4.17 (m, 2H); 4.05 (m, 1H); 3.02 (s, 2H); 2.92 (s, 3H); 2.70 (br.s, 4H); 2.60 (d, J = 6.2 Hz, 2H); 1.94 (m, 2H); 1.84 (m, 2H).
APCI-MS: m/z 447(MH^+).

Example 30

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

Step I:

Ethyl 5-chloro-1'H-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate

A mixture of ethyl 4-oxopiperidine-1-carboxylate (1.71 g, 10 mmol), 4-chlorobenzene-1,2-diol (1.73 g, 12 mmol), and a catalytic amount of 4-methylbenzenesulfonic acid hydrate in dry toluene (30 ml) were refluxed with water separator for 7 h. After cooling, the reaction mixture was washed with 2N sodium hydroxide (2 x 25 ml), and the solvent was removed in vacuo. Flash chromatography on silica gel (heptane/ethyl acetate, 2 : 1) of the residual semi-solid product afforded ethyl 5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate as colourless crystals (0.43 g, 15 %).

APCI-MS: m/z 298 [MH^+].
^{1}H-NMR (400MHz, $CDCl_3$): δ 6.77 (m, 2H), 6.67 (m, 1H), 4.16 (q, 2H, J = 7.1 Hz), 3.67 (t, 4H, J = 5.7 Hz), 1.98 (t, 4H, J = 5.7 Hz), 1.28 (t, 3H, J = 7.1 Hz).

Step II:

5-Chlorospiro[1,3-benzodioxole-2,4'-piperidine]

Ethyl 5-chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidine]-1'-carboxylate (0.43 g, 1.45 mmol) was dissolved in ethanol (5 ml) and water (0.4 ml). Sodium hydroxide (0.2 g) was added followed by reflux for 2 days. After cooling, the solution was concentrated in vacuo, and acidified with 10 % HCl to pH < 1. After the gas evolution had ceased, the solution was made alkaline by addition of saturated aqueous sodium hydrogencarbonate, $NaHCO_3$, and extracted with dichloromethane. Drying with sodium sulphate, Na_2SO_4, and evaporation of the solvent afforded a colourless solid (0.28 g, 1.2 mol, 86 %).

APCI-MS: m/z 226 [MH^+].

^{1}H-NMR (400MHz, $CDCl_3$): δ 6.6 – 6.9 (m, 3H), 3.06 (t, 4H, J = 5.0 Hz), 1.99 (t, 4H, J = 5.2 Hz).

Step III:

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

A solution of 5-chlorospiro[1,3-benzodioxole-2,4'-piperidine] (45 mg, 0.2 mmol) and 4-(acetylamino)-3-[(2*S*)-oxiran-2-ylmethoxy]phenyl acetate (53 mg, 0.2 mmol) in methanol (5 ml) was refluxed for 15 h. The solvent was distilled off under reduced pressure. The residue was purified by preparative HPLC (Kromasil column; eluent: [acetonitrile + 0.1 % trifluoroacetic acid (TFA)/water + 0.1 % TFA]) to afford the titled compound as a colourless solid (37 mg, 0.07 mmol, 33 %).

APCI-MS: m/z 449 [MH^+].

^{1}H-NMR (400MHz, acetone-d_6): δ 8.47 (br. s, 1H), 7.93 (d, 1H, J = 8.7 Hz), 6.8 – 7.0 (m, 3H), 6.53 (d, 1H, J = 2.6 Hz), 6.41 (dd, 1H, J = 2.6 Hz, J = 8.7 Hz), 4.54 (m, 1H), 4.08 (m, 2H), 3.66 (m, 2H), 2.51 (m, 4H), 2.08 (s, 3H), 2.06 (m, 4H).

Example 31

***N*-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate**

The title compound was prepared as described in Example 1 from 5-chlorospiro[1,3-benzodioxole-2,4'-piperidine] (45 mg, 0.2 mmol) and 4-(acetylamino)-3-{[(2*S*)-2-methyloxiran-2-yl]methoxy}phenyl benzoate (68 mg, 0.2 mmol) as a colourless solid (30 mg, 0.05 mmol, 26 %).

APCI-MS: m/z 463 [MH^+].

^{1}H-NMR (400MHz, acetone-d_6): δ 8.59 (br. s, 1H), 7.73 (d, 1H, J = 8.7 Hz), 6.8 – 7.0 (m, 3H), 6.58 (d, 1H, J = 2.6 Hz), 6.42 (dd, 1H, J = 2.6 Hz, J = 8.7 Hz), 4.42 (d, 1H, J = 9.7 Hz), 3.97 (d, 1H, J = 9.7 Hz), 3.71 (d, 1H, J = 14 Hz), 3.54 (d, 1H, J = 14 Hz), 2.52 (m, 4H), 2.09 (s, 3H), 2.06 (m, 4H), 1.51 (s, 3H).

Example 32

***N*-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate**

The title compound was prepared from spiro[1,3-benzodioxole-2,4'-piperidine] (E. K. Moltzen, J. Perrengaard, E. Meier, *J. Med. Chem.* 1995, *38 (11)*, 2009 – 2007) (38 mg, 0.2 mmol) as described Example 30. Yield 78 mg, 0.15 mmol, 74 %.

APCI-MS: m/z 415 [MH^+].

^{1}H-NMR (400MHz, acetone-d_6): δ 7.90 (d, 1H, J = 8.7 Hz), 6.87 (s, 4H), 6.53 (d, 1H, J = 2.6 Hz), 6.75 (dd, 1H, J = 2.6 Hz, , J = 8.7 Hz), 4.56 (m, 1H,), 4.08 (m, 2H), 3.69 (m, 2H), 2.46 (m, 4H), 2.09 (s, 3H), 2.07 (m, 4H).

Example 33

***N*-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-2-methyl-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate**

The title compound was prepared from spiro[1,3-benzodioxole-2,4'-piperidine] (38 mg, 0.2 mmol) as described in Example 31. Yield 88 mg, 0.16 mmol, 81 %.

APCI-MS: m/z 429 [MH^+].

^{1}H-NMR (400MHz, acetone-d_6): δ 7.68 (d, 1H, J = 8.7 Hz), 6.86 (s, 4H), 6.60 (d, 1H, J = 2.5 Hz); 6.43 (dd, 1H, J = 2.6 Hz, J = 8.7 Hz), 4.06 (d, 1H, J = 9.7 Hz), 3.98 (d, 1H, J = 9.7 Hz), 4.03 (d, 1H, J = 9.7 Hz), 3.77 (d, 1H, J = 13.6 Hz), 3.60 (d, 1H, J = 13.6 Hz), 2.51 (m, 4H), 2.10 (s, 3H), 2.08 (m, 4H), 1.52 (s, 3H).

Intermediate Compound: 5-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

Step I:

1'-Benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one

To a solution of 2-bromo-5-chlorobenzoic acid (2.35 g, 10.0 mmol) in tetrahydrofuran (THF) (15 mL) was added, a 1.6 M solution in hexane, n-butyllithium (20 mL, 32.0 mmol) slowly at –78 ^{0}C under nitrogen. After addition was complete the reaction mixture was kept on stirring at –78 ^{0}C for 3 h. Then a solution of 1-benzylpiperidin-4-one (3.78 g, 20.0 mmol) in THF (10 mL) was added slowly to the reaction mixture at –78 ^{0}C. After addition was complete the reaction temperature was raised to room temperature and the reaction mixture was kept on stirring at room temperature overnight. The reaction mixture was poured into a mixture of water (60 mL) and diethyl ether (60 mL), layers were separated. The aqueous layer was extracted with diethyl ether (2 x 20 mL). The aqueous layer was acidified with aqueous 6M hydrochloric acid (HCl) to pH 2 and boiled for 1 h, cooled to 0 ^{0}C, pH was adjusted to 10.0 by addition of aqueous sodium hydroxide (NaOH) (6M) and rapidly extracted with trichloromethane ($CHCl_3$). The organic layer was washed with water, dried over sodium sulphate (Na_2SO_4), filtered and concentrated in vacuo to give the subtitled compound (1.22 g) and it was pure enough for the next step.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.85 (m, 1H); 7.65 (dd, J = 1.9, 8.2 Hz, 1H); 7.41-7.26-1.69 (m, 2H).

APCI-MS: m/z 328(MH^+).

Step II:

1'-Benzyl-5-chloro-3H-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin]-3-one (1.1 g, 3.35 mmol) in THF (12 mL) was added 1 M solution of borane complex in THF (7 mL, 7.0 mmol) slowly at 0 ^{0}C. After addition was complete reaction mixture was kept at room temperature for 30 min, then kept at reflux overnight, cooled to 0 ^{0}C and 6M aqueous HCl (3.5 mL) was added slowly. The reaction mixture was kept at reflux for 5h, cooled to 0 ^{0}C, pH of the reaction mixture was adjusted to 10 by addition of aqueous NaOH (6M) and the whole was extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the subtitled compound (1.0 g).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.40-7.06 (m, 8H); 5.03 (s, 2H); 3.60 (s, 2H), 2.87 (m, 2H); 2.45 (m, 2H); 1.95 (m, 2H); 1.80 (m, 2H).
APCI-MS: m/z 314(MH^+).

Step III:

5-Chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine]

To a solution of 1'-benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (950 mg, 3.02 mmol) in dichloromethane (CH_2Cl_2) (6 mL) was added chloroethyl chloroformate (560.6 mg, 3.92 mmol) slowly at 0 ^{0}C. After addition was complete the reaction mixture was kept on stirring at 0 ^{0}C for 25 min. The volatiles were removed in vacuo, the residue was dissolved in methanol (6 mL) and kept at reflux for 40 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (300 mg) and 1'-benzyl-5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] was recovered (320 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.28-7.24 (m, 2H); 7.18-7.13 (m, 1H); 5.00 (s, 2H); 2.95 (m, 4H); 1.90-1.77 (m, 2H); 1.72-1.63 (m, 2H).
APCI-MS: m/z 224(MH^+).

Intermediate Compound: 5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Step I:

1'-Benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

To a stirring suspension of magnesium strip (763 mg) in diethyl ether (7 mL) was added a crystal of iodine followed by 0.4 mL of 2-(bromomethyl)-1,4-difluorobenzene under nitrogen. The reaction was initiated with a high intensity heat gun, then 2-(bromomethyl)-1,4-difluorobenzene (5.0 g, 24.25 mmol) in diethyl ether (7 mL) was added at such a rate that a gentle reflux was maintained. After addition was complete the reaction mixture was kept on stirring at reflux for 100 min, cooled to room temperature. To this reaction mixture a solution of 1-benzylpiperidin-4-one (4.57 g, 24.25 mmol) in diethyl ether (12 mL) was added dropwise with vigorous stirring. After addition was complete a white cake was formed which was left overnight at room temperature. The cake was hydrolized by treatment with aqueous ammonium chloride (NH_4Cl) solution, extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulphate (Na_2SO_4), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.1% ammonium hydroxide, NH_4OH) to give intermediate compound 1-benzyl-4-(2,5-difluorobenzyl)piperidin-4-ol (2.74 g) containing large amount of impurities. To a suspension of sodium hydride (NaH) (55%, 1.12 g, 26.0 mmol) in toluene (10 mL) was slowly added a solution of 1-benzyl-4-(2,5-difluorobenzyl)piperidin-4-ol in toluene (15 mL). After addition was complete, the reaction mixture was kept on stirring at 110 ^{0}C (in a preheated oil bath), after 5 minutes dimethylformamide (9 mL) was added and stirring was continued at reflux for 2h. The reaction mixture was cooled to room temperature, water (20 mL) was added and extracted with ethyl acetate. The organic layer was dried over sodium sulphate (Na_2SO_4), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.1% ammonium hydroxide, NH_4OH) to give the subtitled compound (190 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.39-7.26 (m, 5H); 6.88-6.76 (m, 2H); 6.67 (dd, J = 4.2, 8.7 Hz, 1H); 3.59 (s, 2H); 2.99 (s, 2H); 2.68-2.47 (m, 4H); 2.03-1.94 8M, 2H); 1.86-1.76 (m, 2H).

APCI-MS: m/z 298(MH^+).

Step II:

5-Fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine]

Ethyl chloroformate (65.6mg, 0.604 mmol) was added to a solution of 1'-benzyl-5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (150 mg, 0.504 mmol) in toluene (2 mL) and the reaction mixture was refluxed overnight. The reaction mixture was cooled to room temperature, diluted by addition of toluene, washed successively with aqueous sodium hydrogencarbonate ($NaHCO_3$) and water. The organic layer was dried over sodium sulphate (Na_2SO_4) filtered and concentrated in vacuo. The residue was dissolved in ethanol (3.5 mL), aqueous potassium hydroxide (KOH) (800mg KOH in 0.8 mL water) was added and the reaction mixture was kept on stirring at reflux overnight, cooled to room temperature, extracted with ethyl acetate. The organic layer was well washed with water, dried over sodium sulphate (Na_2SO_4), filtered and concentrated. The residue was purified by HPLC (10% acetonitrile (CH_3CN)-55% CH_3CN in water containing 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (49 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 6.92-6.87 (m, 1H); 6.81-6.75 (m, 1H); 6.64 (dd, J = 4.2, 8.7 Hz, 1H); 3.08-2.98 (m, 4H); 2.89-2.81 (m, 2H); 1.92-1.83 (m, 2H); 1.78-1.71 (m, 2H).

APCI-MS: m/z 208(MH^+).

Intermediate Compound: 5-Chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]

Step I:

1-Benzyl-3-(5-chloro-2-fluorobenzyl)pyrrolidin-3-ol

To a stirring suspension of magnesium strip (1.39 g, 57.06 mmol) in diethyl ether (10 mL) was added a crystal iodine followed by 0.5 mL of 2-(bromomethyl)-4-chloro-1-

fluorobenzene under nitrogen. The reaction was initiated with a high intensity heat gun, then a solution of 2-(bromomethyl)-4-chloro-1-fluorobenzene (12.75 g, 57.06 mmol) in diethyl ether was added at such a speed that gentle reflux was maintained. After addition was complete the reaction mixture was kept on stirring at reflux for 3.5 h, cooled to room temperature and a solution of 1-benzylpyrrolidin-3-one (10.0 g, 57.06 mmol) in diethyl ether (20 mL) was added dropwise with vigorous stirring. After addition was complete the reaction mixture was left overnight at room temperature. This reaction mixture was treated with aqueous ammonium chloride (NH_4Cl) solution and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate (Na_2SO_4), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (650 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.39-7.23 (m, 6H); 7.21-7.15 (m, 1H); 6.98 (t, J = 9.0 Hz, 1H); 3.68 (d, J = 13.0 Hz, 1H); 3.63 (d, J = 13.0 Hz, 1H); 3.01-2.89 (m, 3H); 2.65 (d, J = 9.5 Hz, 1H); 2.42-2.34 (m, 2H); 2.07-1.98 (m, 1H); 1.88-1.75 (m, 1H); 1.64 (br.s, 1H). APCI-MS: m/z 320(MH^+).

Step II:

1'-Benzyl-5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]

To a suspension of sodium hydride (NaH) (55%, 612 mg, 14.0 mmol) in toluene (10 mL) was added a solution of 1-benzyl-3-(5-chloro-2-fluorobenzyl)pyrrolidin-3-ol (1.3 g, 4.06 mmol) in toluene (20 mL) and the reaction mixture was kept on stirring at reflux, after 5 minutes dimethylformamide (10 mL) was added and the reaction mixture was refluxed for 90 minutes, cooled to room temperature, water (20 mL) was added and extracted with ethyl acetate. The organic layer was dried over sodium sulphate (Na_2SO_4), filtered, concentrated and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (560 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.39-7.24 (m, 5H); 7.10 (s, 1H); 7.06 (dd, J = 2.3, 8.5 Hz, 1H); 6.68 (d, J = 8.4 Hz, 1H); 3.73 (d, J = 13.0 Hz, 1H); 3.70 (d, J = 13.0 Hz, 1H); 3.24 (d, J = 16.0 Hz, 1H); 3.20 (d, J = 16.0 Hz, 1H); 2.99 (d, J = 10.4 Hz, 1H); 2.95-2.88 (m, 1H); 2.74-2.64 (m, 2H); 2.43-2.34 (m, 1H); 2.11-2,02 (m, 1H).

APCI-MS: m/z 300(MH^+).

Step III:

5-Chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine]

The experimental procedure is the same as described above for the corresponding piperidine derivative using 1'-benzyl-5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (555 mg, 1.85 mmol), ethyl chloroformate (261 mg, 2.4 mmol), toluene (5 mL), potassium hydroxide (KOH) (3.0 g), water (3 mL) and ethanol (6 mL) to give the titled compound (240 mg) after silica gel flash chromatography (0-2% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.13 (s, 1H); 7.08 (dd, J = 2.3, 8.5 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 3.32-3.16 (m, 4H); 3.07 (ddd, J = 4.8, 9.1, 11.2 Hz, 1H); 2.80 (d, J =12.3 Hz, 1H); 2.33-2.24 (m, 1H); 1.93 (ddd, J = 7.3, 9.1, 13.7 Hz, 1H).

APCI-MS: m/z 210(MH^+).

Example 34

***N*-(2-{[(2S)-3-(5-Chloro-1'H,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] (29.3 mg, 0.131 mmol) and 4-(acetylamino)-3-[(2S)-oxiran-2-ylmethoxy]phenyl acetate (35 mg, 0.131 mmol) in ethanol (1.5 mL) was kept on stirring at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by HPLC (acetonitrile (CH_3CN) 10-55% in water, 0.1% trifluoroacetic acid, CF_3COOH) to give the titled compound (35 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.36 (m, 3H); 7.21 (d, J = 8.7 Hz, 1H); 6.50 (d, J = 2.4 Hz, 1H); 6.40 (dd, J = 2.4, 8.7 Hz, 1H); 5.10 (s, 2H); 4.48 (m, 1H); 4.05 (d, J = 4.6 Hz, 2H); 3.78-3.63 (m, 2H); 3.56-3.35 (m, 4H); 2.40-2.21 (m, 2H); 2.13 (s, 3H); 2.08-1.95 (m, 2H).

APCI-MS: m/z 447(MH^+).

Example 35

***N*-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidin] (35 mg, 0.156 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (32.3 mg, 0.156 mmol) in ethanol (1.5 mL) was kept on stirring at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (45 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.99 (dd, J = 1.3, 7.9 Hz, 1H); 7.29-7.25 (m, 2H); 7.18 (d, J = 7.8 Hz, 1H); 7.12-7.01 (m, 2H); 6.96-6.91 (m, 1H); 5.00 (s, 2H); 4.25 (m, 1H); 4.13 (dd, J = 3.2, 9.9 Hz, 1H); 3.99 (dd, J = 6.4, 9.9 Hz, 1H); 3.00-2.89 (m, 2H); 2.67-2.50 (m, 4H); 2.20 (s, 3H); 2.08-1.96 (m, 2H); 1.73 (m, 2H).

APCI-MS: m/z 431(MH^+).

Example 36

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

Step I:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (26 mg, 0.116 mmol) and 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (40 mg, 0.116 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.1% ammonium hydroxide, NH_4OH) to give the subtitled compound (50 mg).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 78.18 (d, J = 8.8 Hz, 1H); 8.14 (m, 1H); 7.37 (d, J = 8.7 Hz, 2H); 7.28 (m, 2H); 7.22 (s, 1H); 7.09 (d, J = 8.0 Hz, 1H); 6.97-6.92 (m, 2H); 6.71 (dd, J = 2.3, 8.8 Hz, 1H); 6.52 (d, J = 2.3 Hz, 1H); 5.08 (s, 2H); 5.05 (s, 2H); 4.25-4.15 (m, 2H); 3.85 (s, 3H); 3.00 (m, 4H); 2.88-2.75 (m, 2H); 2.66-2.46 (m, 3H); 2.06-1.90 (m, 2H); 1.82 (d, J = 12.9 Hz, 2H).
APCI-MS: m/z 567(MH^+).

Step II:
2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide
2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (45 mg, 0.079 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC (10-45% acetonitrile (CH_3CN) in water, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (17 mg).

^{1}H-NMR (CD_3OD, 400 MHz): δ 7.82 (d, J = 8.7 Hz, 1H); 7.30-7.25 (m, 2H); 7.18 (d, J = 7.9 Hz, 1H); 6.55 (d, J = 2.2 Hz, 1H); 6.48 (dd, J = 2.2, 8.7 Hz, 1H); 5.05 (s, 2H); 4.26-4.19 (m, 2H); 4.09-4.04 (m, 1H); 2.98-2.87 (m, 5H); 2.64-2.50 (m, 4H); 2.09-1.97 (m, 2H); 1.73 (d, J = 13.2 Hz, 2H).
APCI-MS: m/z 447(MH^+).

Example 37

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

Step I:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide

A mixture of 5-chloro-3*H*-spiro[2-benzofuran-1,4'-piperidine] (40 mg, 0.178 mmol) and *N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]-2-{[(2S)-2-methyloxiran-2-yl]methoxy}benzamide (68 mg, 0.178 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C for 6h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-0.9% methanol in dichloromethane, 0.1% ammonium hydroxide, NH_4OH) to give the subtitled compound (45 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 8.21 (br.s, 1H); 7.99 (d, J = 8.7 Hz, 1H); 7.36 (d, J = 8.7 Hz, 2H)7.27 (m, 1H); 7.20 (s, 1H); 7.03 (d, J = 8.0 Hz, 1H); 6.92 (m, 2H); 6.70 (dd, J = 2.3, 8.8 Hz, 1H); 6.50 (d, J = 2.3 Hz, 1H); 5.03 (s, 2H); 5.01 (s, 2H); 3.86 (s, 2H); 2.85 (s, 3H); 3.05 (m, 1H); 2.91-2.80 (m, 3H); 2.75 (m, 1H); 2.67 (d, J = 13.9 Hz, 1H); 2.50 (d, J = 13.9 Hz, 1H); 1.95 (m, 2H); 1.75 (m, 2H); 1.30 (s, 3H); 0.83 (m, 2H); 0.62 (m, 2H).

APCI-MS: m/z 607(MH^+).

Step II:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide

2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-[(4-methoxybenzyl)oxy]benzamide (40 mg, 0.065 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC (10-55% acetonitrile (CH_3CN) in water, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (30 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.84 (d, J = 8.4 Hz, 1H); 7.25 (m, 2H); 7.16 (d, J = 7.6 Hz, 1H); 6.45 (m, 2H); 5.00 (s, 2H); 4.11 (d, J = 9.0 Hz, 1H); 3.93 (d, J = 9.0 Hz, 1H); 2.93 (m, 1H); 2.88 (m, 2H); 2.74-2.49 (m, 4H); 1.99 (m, 2H); 1.62 (m, 2H); 1.31 (s, 3H); 0.79 (m, 2H); 0.65 (m, 2H).

APCI-MS: m/z 487(MH^+).

Example 38

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)benzamide

Step I:

Methyl-4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate

A mixture of 2(S)-oxiran-2-ylmethyl3-nitrobenzenesulfonate (518 mg, 2.0 mmol), methyl 2-hydroxy-4-[(4-methoxybenzyl)oxy]benzoate (576.6 mg, 2.0 mmol) and cesium carbonate (Cs_2CO_3) (812.5 mg, 2.5 mmol) in dimethylformamide (10 mL) was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulphate, Na_2SO_4, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-30% ethyl acetate in petroleum ether) to give the subtitled compound (600 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 7.87 (d, J = 8.7 Hz, 1H); 7.39-7.34 (m, 2H); 6.97-6.92 (m, 2H); 6.61 (dd, J = 2.4, 8.7 Hz, 1H); 6.59 (d, J = 2.2 Hz, 1H); 5.04 (s, 2H); 4.31 (dd, J = 2.9, 11.1 Hz, 1H); 4.07 (dd, J = 4.8, 11.1 Hz, 1H); 3.88 (s, 3H); 3.85 (s, 3H); 3.40 (m, 1H); 2.92 (m, 2H).

APCI-MS: m/z 345(MH^+).

Step II:

Methyl 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate

A mixture of 5-chloro-3H-spiro[1-benzofuran-2,4'-piperidine] (150 mg, 0.67 mmol) and methyl-4-[(4-methoxybenzyl)oxy]-2-[(2S)-oxiran-2-ylmethoxy]benzoate (230.5 mg, 0.67 mmol) in ethanol (3 mL) was stirred at 80 °C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane) to give the subtitled compound (370 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 7.87 (d, J = 8.8 Hz, 1H); 7.40-7.35 (m, 2H); 7.12 (m, 1H); 7.07 (dd, J = 2.2, 8.4 Hz, 1H); 6.98-6.93 (m, 2H); 6.69 (d, J = 8.4 Hz, 1H); 6.63 (d, J = 2.2 Hz, 1H); 6.60 (s, 1H); 5.06 (s, 2H); 4.19 (m, 2H); 4.03 (m, 1H); 3.89 (s, 3H); 3.85 (s, 3H); 3.00 (s, 2H); 2.80 (m, 1H); 2.73-2.58 (m, 5H); 2.00 (m, 2H); 1.82 (m, 2H).
APCI-MS: m/z 568(MH^+).

Step III:
2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(2-hydroxyethyl)-4-[(4-methoxybenzyl)oxy]benzamide
A mixture of methyl2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate (60 mg, 0.105 mmol) and 2-aminoethanol (0.256 mL, 4.2 mmol) in methanol (2 mL) was refluxed for 72h. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (30 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 8.49 (t, *J* = 5.4 Hz, 1H); 8.17 (d, *J* = 8.8 Hz, 1H); 7.40-7.35 (m, 2H); 7.12 (s, 1H); 7.09 (dd, *J* = 2.2, 8.4 Hz, 1H); 6.98-6.93 (m, 2H); 6.72 (dd, *J* = 2.2, 8.8 Hz, 1H); 6.69 (d, *J* = 8.5 Hz, 1H); 6.55 (d, *J* = 2.2 Hz, 1H); 5.06 (s, 2H); 4.21 (m, 2H); 3.94 (dd, *J* = 7.2, 10.1 Hz, 1H); 3.85 (s, 3H); 3.83 (d, *J* = 4.8 Hz, 2H); 3.70 (m, 1H); 3.60 (m, 1H); 3.00 (s, 2H); 2.91-2.76 (m, 2H); 2.68-2.53 (m, 4H); 2.00 (m, 2H); 1.80 (m, 2H).
APCI-MS: m/z 597(MH^+).

Step IV:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)benzamide

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-(2-hydroxyethyl)-4-[(4-methoxybenzyl)oxy]benzamide (27 mg, 0.045 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) for 30 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-4% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (16 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.85 (d, J = 8.6 Hz, 1H); 7.13 (m, 1H); 7.19 (dd, J = 2.4, 8.5 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 6.52 (d, J = 2.2 Hz, 1H); 6.49 (dd, J = 2.2, 8.6 Hz, 1H); 4.27-4.17 (m, 2H); 4.06 (dd, J = 5.9, 9.4 Hz, 1H); 3.73 (t, J = 5.6 Hz, 2H); 3.53 (m, 2H); 3.00 (s, 2H); 2.70 (m, 4H); 2.62 (d, J = 6.4 Hz, 2H); 1.95 (m, 2H); 1.84 (m, 2H). APCI-MS: m/z 477(MH^+).

Example 39

***N*-(2-Aminoethyl)-2-{](2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide**

Step I:

***N*-(2-Aminoethyl)-2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzamide**

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (50 mg, 0.084 mmol) and *N*,*N*-carbonyldiimidazole (14 mg, 0.084 mmol) in dimethylformamide (3 mL) was kept on stirring at room temperature for 1h. Then ethylenediamine (11 mg, 0.168 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over

sodium sulphate, Na_2SO_4, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (22 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.93 (d, J = 8.9 Hz, 1H); 7.45 (m, 2H); 7.12 (s, 1H); 7.04(dd, J = 2.3, 8.6 Hz, 1H); 6.95-6.90 (m, 2H); 6.73 (s, 1H); 6.70 (d, J = 2.2 Hz, 1H); 6.64 (d, J = 8.5 Hz, 1H); 5.08 (s, 2H); 4.27 (dd, J = 2.7, 9.7 Hz, 1H); 4.23-4.15 (m, 1H); 4.05 (dd, J = 6.6, 9.8 Hz, 1H); 3.80 (s, 3H); 3.48 (t, J = 5.9 Hz, 2H); 2.96 (s, 2H); 2.86 (t, J = 6.1 Hz, 2H); 2.68 (m, 4H); 2.56 (d, J = 6.4 Hz, 2H); 1.90 (m, 2H); 1.80 (m, 2H).
APCI-MS: m/z 596(MH^+).

Step II:

_N_-(2-Aminoethyl)-2-{](2S)-3-(5-chloro-1'_H_,3_H_-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide

_N_-(2-Aminoethyl)-2-{[(2S)-3-(5-chloro-1'_H_,3_H_-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzamide ((22mg, 0.037 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (2 mL) for 20 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC (10-60% acetonitrile (CH_3CN) in water, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (8 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.83 (d, J = 8.6 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, J = 2.2, 8.4 Hz, 1H); 6.65 (d, J = 8.4 Hz, 1H); 6.50 (d, J = 2.1 Hz, 1H); 6.47 (dd, J = 2.2, 8.6 Hz, 1H); 4.27-4.19 (m, 2H); 4.04 (m, 1H); 3.50 (t, J = 6.0 Hz, 2H); 3.02 (s, 2H); 2.90 (t, J = 6.0 Hz, 2H); 2.69 (m, 4H); 2.60 (d, J = 6.2 Hz, 2H); 1.94 (m, 2H); 1.84 (m, 2H).
APCI-MS: m/z 476(MH^+).

Example 40

2-{[(2S)-3-(5-Fluoro-1'_H_,3_H_-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-_N_-methylbenzamide

Step I:

2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (20 mg, 0.096 mmol) and 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (34.3 mg, 0.099 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-0.8% methanol in dichloromethane, 0.1% ammonium hydroxide, NH_4OH) to give the subtitled compound (36 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 8.16 (d, J = 8.7 Hz, 1H); 8.10 (m, 1H); 7.36 (m, 2H); 6.96-6.91 (m, 2H); 6.89-6.77 (m, 2H); 7.72-6.64 (m, 2H); 6.54 (d, J = 2.3 Hz, 1H); 5.00 (s, 2H); 4.20-4.10 (m, 2H); 3.96 (dd, J = 5.4, 9.4 Hz, 1H); 3.83 (s, 3H); 3.01 (s, 3H); 3.00 (s, 2H); 2.90 (m, 1H); 2.80 (m, 1H); 2.64-2.50 (m, 4H); 2.00 (m, 2H); 1.83 (m, 2H).
APCI-MS: m/z 551(MH^+).

Step II:

2-{[(2S)-3-(5-fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (32 mg, 0.058 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (2.5 mL) for 20 min at room temperature. The volatiles were removed in vacuo and the residue was purified by HPLC (10-50% acetonitrile (CH_3CN) in water, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (11 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 7.82 (d, J = 8.6 Hz, 1H); 6.50 (dd, J = 2.7, 8.1 Hz, 1H); 6.81-6.74 (m, 1H); 6.62 (dd, J = 4.2, 8.7 Hz, 1H); 6.52 (d, J = 2.2 Hz, 1H); 6.48 (dd, J =

2.2, 8.6 Hz, 1H); 4.24-4.17 (m, 2H); 4.08-4.02 (m, 1H); 3.01 (s, 2H); 2.92 (s, 3H); 2.77-2.63 (m, 4H); 2.60 (d, J = 6.2 Hz, 2H); 1.94 (m, 2H); 1.84 (m, 2H).
APCI-MS: m/z 431(MH^+).

Example 41

***N*-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide**

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (20 mg, 0.096 mmol) and 4-(acetylamino)-3-[(2S)-oxiran-2-ylmethoxy]phenyl acetate (25.5 mg, 0.096 mmol) in ethanol (2 mL) was kept on stirring at 80 ^{0}C over the weekend. The volatiles were removed in vacuo and the residue was purified by HPLC (10-35% acetonitrile (CH_3CN) in water, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (14 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.57 (d, J = 8.7 Hz, 1H); 6.90 (m, 1H); 6.81-6.74 (m, 1H); 6.63 (dd, J = 4.2, 8.7 Hz, 1H); 6.48 (d, J = 2.5 Hz, 1H); 6.36 (dd, J = 2.6, 8.7 Hz, 1H); 4.18 (m, 1H); 4.05 (dd, J = 3.4, 9.8 Hz, 1H); 3.93 (dd, J = 6.2, 9.8 Hz, 1H); 3.01 (s, 2H); 2.70 (m, 4H); 2.61 (t, J = 7.0 Hz, 2H); 2.14 (s, 3H); 1.96 (m, 2H); 1.85 (m, 2H).
APCI-MS: m/z 431(MH^+).

Example 42

***N*-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide**

A mixture of 5-fluoro-3*H*-spiro[1-benzofuran-2,4'-piperidine] (8 mg, 0.038 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (8 mg, 0.038 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by HPLC (10-70% acetonitrile (CH_3CN) in water, 0.1% ammonium hydroxide, NH_4OH) to give the titled compound (11 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.99 (dd, J = 1.5, 8.1 Hz, 1H); 7.08 (m, 1H); 7.03 (m, 1H); 6.94 (m, 1H); 6.90 (m, 1H); 6.77 (m, 1H); 6.63 (dd, J = 4.2, 8.8 Hz, 1H); 4.19 (m, 1H); 4.12 (dd, J = 3.2, 9.9 Hz, 1H); 3.98 (dd, J = 6.4, 9.9 Hz, 1H); 3.05 (s, 2H); 2.70 (m, 4H); 2.62 (m, 2H); 2.19 (s, 3H); 1.94 (m, 2H); 1.85 (m, 2H).

APCI-MS: m/z 415(MH^+).

Example 43

***N*-[2-({(2S)-3[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (34.5 mg, 0.167 mmol) and *N*-{2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (35 mg, 0.167 mmol) in ethanol (1.5 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol (CH_3OH) in dichloromethane (CH_2Cl_2), 0.2% ammonium hydroxide, NH_4OH) to give a mixture of two isomers (55 mg). This mixture was subjected to chiral HPLC to give the titled compound (17 mg) and other isomer (14 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.99 (dd, J = 1.4, 8.0 Hz, 1H); 7.15 (m, 1H); 7.11-7.01 (m, 3H); 6.93 (m, 1H); 6.66 (d, J = 8.5 Hz, 1H); 4.18-4.11 (m, 2H); 3.99 (dd, J = 7.0, 10.6 Hz, 1H); 3.25 (m, 2H); 3.11 (d, J = 10.8 Hz, 1H); 3.00 (m, 1H); 2.86-2.69 (m, 4H); 2.33-2.25 (m, 1H); 2.18 (s, 3H); 2.13-2.05 (m, 1H).

APCI-MS: m/z 417(MH^+).

Example 44

***N*-[2-({(2S)-3[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide**

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.99 (dd, J = 1.4, 8.0 Hz, 1H); 7.15 (m, 1H); 7.11-7.01 (m, 3H); 6.93 (m, 1H); 6.66 (d, J = 8.5 Hz, 1H); 4.18-4.11 (m, 2H); 3.99 (dd, J = 7.0, 10.6

Hz, 1H); 3.25 (m, 2H); 3.11 (d, J = 10.8 Hz, 1H); 3.00 (m, 1H); 2.86-2.69 (m, 4H); 2.33-2.25 (m, 1H); 2.18 (s, 3H); 2.13-2.05 (m, 1H).

APCI-MS: m/z 417(MH^+).

Example 45

***N*-[2-({(2S)-3-[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide**

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (60 mg, 0.286 mmol) and *N*-{4-methoxy-2-[(2S)-oxiran-2-ylmethoxy]phenyl}acetamide (68 mg, 0.286 mmol) in ethanol (2 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol (CH_3OH) in dichloromethane (CH_2Cl_2), 0.2% ammonium hydroxide, NH_4OH) to give a mixture of two isomers and this was subjected to chiral HPLC to give the titled compound (35 mg) and the other isomer (35 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.73 (d, J = 8.8 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, J = 2.2, 8.4 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 6.60 (d, J = 2.5 Hz, 1H); 6.49 (dd, J = 2.6, 8.8 Hz, 1H); 4.15-4.06 (m, 2H); 3.96 (dd, J = 6.2, 9.8 Hz, 1H); 3.79 (s, 3H); 3.25 (m, 2H); 3.11 (dd, J = 10.7, 15.9 Hz, 1H); 2.99 (m, 1H); 2.85-2.64 (m, 4H); 2.25 (m, 1H); 2.13 (s, 3H); 2.08 (m, 1H).

APCI-MS: m/z 447(MH^+).

Example 46

***N*-[2-({(2S)-3-[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide**

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.73 (d, J = 8.8 Hz, 1H); 7.14 (m, 1H); 7.04 (dd, J = 2.2, 8.4 Hz, 1H); 6.65 (d, J = 8.5 Hz, 1H); 6.60 (d, J = 2.5 Hz, 1H); 6.49 (dd, J = 2.6, 8.8 Hz, 1H); 4.15-4.06 (m, 2H); 3.96 (dd, J = 6.2, 9.8 Hz, 1H); 3.79 (s, 3H); 3.25 (m, 2H); 3.11

(dd, J = 10.7, 15.9 Hz, 1H); 2.99 (m, 1H); 2.85-2.64 (m, 4H); 2.25 (m, 1H); 2.13 (s, 3H); 2.08 (m, 1H).

APCI-MS: m/z 447(MH^+).

Example 47

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

Step I:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide

A mixture of 5-chloro-3*H*-spiro[1-benzofuran-2,3'-pyrrolidine] (80 mg, 0.381 mmol) and 4-[(4-methoxybenzyl)oxy]-*N*-methyl-2-[(2S)-oxiran-2-ylmethoxy]benzamide (130.8 mg, 0.381 mmol) in ethanol (3 mL) was stirred at 80 ^{0}C overnight. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-1% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (165 mg).

^{1}H-NMR ($CDCl_3$), 400 MHz): δ 8.15 (d, J = 8.8 Hz, 1H); 8.04 (m, 1H); 7.36 (m, 2H); 7.13 (br,s, 1H); 7.09 (m, 1H); 6.93 (m, 2H); 6.72-6.66 (m, 2H); 6.54 (d, J = 2.2 Hz, 1H); 5.05 (s, 2H); 4.17 (dd, J = 3.2, 9.5 Hz, 1H); 4.09 (m, 1H); 3.98 (dd, J = 5.7, 9.5 Hz, 1H); 3.83 (s, 3H); 3.30-2.83 (m, 9H); 2.72 (m, 1H); 2.60 (dd, J = 3.4, 12.1 Hz, 1H); 2.34 (m, 2H); 2.08 (m, 2H).

APCI-MS: m/z 553(MH^+).

Step II:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]-*N*-methylbenzamide (160 mg, 0.289 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol (CH_3OH) in dichloromethane (CH_2Cl_2), 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (80 mg).

APCI-MS: m/z 433(MH^+).

Example 48

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (trifluoroacetate)

Step I:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl]benzoic acid

To a solution of methyl 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoate (150 mg, 0.264 mmol) in ethanol (2 mL) was added aqueous solution of potassium hydroxide (KOH) (770 mg, KOH in 0.77 mL water) and the reaction mixture was stirred at reflux overnight, cooled to 0 ^{0}C and the pH was adjusted to 2.0 by addition of aqueous hydrochloric acid (HCl). The whole was extracted with ethyl acetate. The organic layer was dried over sodium sulphate, Na_2SO_4, filtered and concentrated to give the subtitled compound (145 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.78 (d, J = 8.4 Hz, 1H); 7.35 (m, 2H); 7.19 (m, 1H); 7.09 (dd, J = 2.2, 8.4 Hz, 1H); 6.93 (m, 2H); 6.75-6.65 (m, 3H); 5.09 (s, 2H); 4.40 (m, 1H); 4.24 (dd, J = 4.0, 9.3 Hz, 1H); 4.06 (dd, J = 5.5, 9.3 Hz, 1H); 3.80 (s, 3H); 3.70-3.53 (m, 2H); 3.51-3.35 (m, 4H); 3.14 (s, 2H); 2.33 (m, 2H); 2.12 (d, J = 14.8 Hz, 2H).
APCI-MS: m/z 554(MH^+).

Step II:

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (trifluoroacetate)

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl]benzoic acid (31 mg, 0.052 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (2 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified by HPLC (10-55% acetonitrile (CH_3CN) in water, 0.1% trifluoroacetic acid (CF_3COOH)) to give the titled compound (15 mg).

APCI-MS: m/z 434(MH^+).

Example 49

3(S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

Step I:

(3S)-1-{2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (100 mg, 0.169 mmol) and *N*,*N*-carbonyldiimidazole (30 mg, 0.186 mmol) in dimethylformamide (3mL) was stirred at room temperature for 1h. Then (3S)-pyrrolidin-3-ol (76.3 mg, 0.845 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over sodium sulphate, Na_2SO_4, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-2.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (55 mg).

APCI-MS: m/z 623(MH^+).

Step II:

3(S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

(3S)-1-{2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol (50 mg, 0.08 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-4.5% methanol (CH_3OH) in dichloromethane (CH_2Cl_2), 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (25 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.13 (m, 1H); 7.08 (dd, J = 2.5, 8.2 Hz, 1H); 7.03 (dd, J = 2.3, 8.5 Hz, 1H); 6.65 (d, J = 8.4 Hz, 1H); 6.49 (m, 1H); 6.44 (m, 1H); 4.48 (m, 0.5 H); 4.35 (m, 0.5H); 4.10 (m, 1H); 4.03 (m, 1H); 3.96 (dd, J = 5.6, 9.7 Hz, 1H); 3.67 (m, 1H); 3.62-3.50 (m, 2H); 3.30 (m, 1H); 3.00 (s, 2H); 2.78-2.52 (m, 6H); 2.12-1.77 (m, 6H). APCI-MS: m/z 503(MH^+).

Example 50

3(R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

Step I:

(3R)-1-{2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (60 mg, 0.101 mmol) and *N*,*N*-carbonyldiimidazole (17.5 mg, 0.108 mmol) in dimethylformamide (3mL) was stirred at room temperature for 1h. Then (3R)-pyrrolidin-3-ol (47 mg, 0.540 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was

partitioned between ethyl acetate and water, the organic layer was dried over sodium sulphate, Na_2SO_4, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (64 mg).

APCI-MS: m/z 623(MH^+).

Step II:

3(R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol

(3R)-1-{2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(4-methoxybenzyl)oxy]benzoyl}pyrrolidin-3-ol (60mg, 0.096 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) at room temperature for 20 min. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-5% methanol (CH_3OH) in dichloromethane (CH_2Cl_2), 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (8 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.13 (m, 1H); 7.08 (dd, J = 2.5, 8.2 Hz, 1H); 7.03 (dd, J = 2.3, 8.5 Hz, 1H); 6.65 (d, J = 8.4 Hz, 1H); 6.49 (m, 1H); 6.44 (m, 1H); 4.48 (m, 0.5 H); 4.35 (m, 0.5H); 4.10 (m, 1H); 4.03 (m, 1H); 3.96 (dd, J = 5.6, 9.7 Hz, 1H); 3.67 (m, 1H); 3.62-3.50 (m, 2H); 3.30 (m, 1H); 3.00 (s, 2H); 2.78-2.52 (m, 6H); 2.12-1.77 (m, 6H).
APCI-MS: m/z 503(MH^+).

Example 51

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(morpholin-4-ylcarbonyl)phenol

Step I:

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-{5-[(4-methoxybenzyl)oxy]-2-(morpholin-4-ylcarbonyl)phenoxy}propan-2-ol

A mixture of 2-{[(2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (100 mg, 0.169 mmol) and *N*,*N*-carbonyldiimidazole (35 mg, 0.215 mmol) in dimethylformamide (3mL) was stirred at room temperature for 1h. Then morpholine (250 mg, 2.86 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer was dried over sodium sulphate, Na_2SO_4, filtered, concentrated in vacuo and the residue was purified by silica gel flash chromatography (0-1.5% methanol in dichloromethane, 0.2% ammonium hydroxide, NH_4OH) to give the subtitled compound (58 mg).

APCI-MS: m/z 623 (MH^+).

Step II:

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(morpholin-4-ylcarbonyl)phenol

(2S)-1-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-3-[5-[(4-methoxybenzyl)oxy]-2-(morpholin-4-ylcarbonyl)phenoxy]propan-2-ol (55 mg, 0.088 mmol) was treated with 10% trifluoroacetic acid (CF_3COOH) in dichloromethane (CH_2Cl_2) (3 mL) for 25 min at room temperature. The volatiles were removed in vacuo and the residue was purified by silica gel flash chromatography (0-3% methanol (CH_3OH) in dichloromethane (CH_2Cl_2), 0.2% ammonium hydroxide, NH_4OH) to give the titled compound (24 mg).

^{1}H-NMR (CD_3OD), 400 MHz): δ 7.13 (m, 1H); 7.07-7.01 (m, 2H); 6.65 (d, J = 8.5 Hz, 1H); 6.50 (d, J = 2.1 Hz, 1H); 6.45 (dd, J = 2.1, 8.2 Hz, 1H); 4.15-3.92 (m, 3H); 3.87-3.37 (m, 8H); 3.00 (s, 2H); 2.78-2.49 (m, 6H); 1.94 (m, 2H); 1.83 (m, 2H).

APCI-MS: m/z 503(MH^+).

THP-1 Chemotaxis Assay

Introduction

The assay measured the chemotactic response elicited by MIP-1α chemokine in the human monocytic cell line THP-1. The compounds of the Examples were evaluated by their ability to depress the chemotactic response to a standard concentration of MIP-1α chemokine.

Methods

Culture of THP-1 cells

Cells were thawed rapidly at 37°C from frozen aliquots and resuspended in a 25 cm flask containing 5 ml of RPMI-1640 medium supplemented with Glutamax and 10% heat inactivated fetal calf serum without antibiotics (RPMI+10%HIFCS). At day 3 the medium is discarded and replaced with fresh medium.

THP-1 cells are routinely cultured in RPMI-1640 medium supplemented with 10% heat inactivated fetal calf serum and glutamax but without antibiotics. Optimal growth of the cells requires that they are passaged every 3 days and that the minimum subculture density is $4x10^5$ cells/ml.

Chemotaxis assay

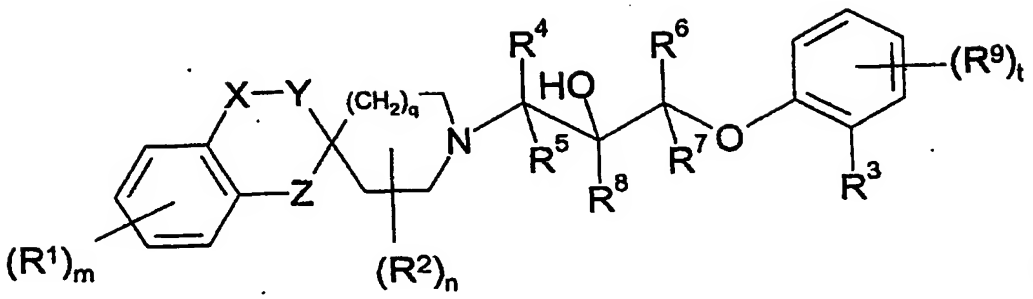
Cells were removed from the flask and washed by centrifugation in RPMI+10%HIFCS+glutamax. The cells were then resuspended at $2x10^7$ cells/ml in fresh medium (RPMI+10%HIFCS+glutamax) to which was added calcein-AM (5 µl of stock solution to 1 ml to give a final concentration of $5x10^{-6}$M). After gentle mixing the cells were incubated at 37°C in a CO_2 incubator for 30 minutes. The cells were then diluted to 50 ml with medium and washed twice by centrifugation at 400xg. Labelled cells were then resuspended at a cell concentration of $1x10^7$ cells/ml and incubated with an equal volume

of MIP-1α antagonist (10^{-10}M to 10^{-6}M final concentration) for 30 minutes at 37°C in a humidified CO_2 incubator.

Chemotaxis was performed using Neuroprobe 96-well chemotaxis plates employing 8 μm filters (cat no. 101-8). Thirty microlitres of chemoattractant supplemented with various concentrations of antagonists or vehicle were added to the lower wells of the plate in triplicate. The filter was then carefully positioned on top and then 25μl of cells preincubated with the corresponding concentration of antagonist or vehicle were added to the surface of the filter. The plate was then incubated for 2 hours at 37°C in a humidified CO_2 incubator. The cells remaining on the surface were then removed by adsorption and the whole plate was centrifuged at 2000 rpm for 10 minutes. The filter was then removed and the cells that had migrated to the lower wells were quantified by the fluorescence of cell associated calcein-AM. Cell migration was then expressed in fluorescence units after subtraction of the reagent blank and values were standardized to % migration by comparing the fluorescence values with that of a known number of labelled cells. The effect of antagonists was calculated as % inhibition when the number of migrated cells were compared with vehicle.

CLAIMS

1. A compound of formula



(I)

wherein

m is 0, 1, 2, 3 or 4;

each R^1 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or sulphonamido;

either X represents a bond, -CH_2-, -O- or -C(O)- and Y represents a bond, -CH_2-, -O- or -C(O)-, or X and Y together represent a group -CH=C(CH_3)- or -C(CH_3)=CH-, and Z represents a bond, -O-, -NH- or -CH_2-, provided that only one of X, Y and Z can represent a bond at any one time and provided that X and Y do not both simultaneously represent –O- or -C(O)-;

n is 0, 1 or 2;

each R^2 independently represents halogen or C_1-C_6 alkyl;

q is 0 or 1;

R^3 represents -$NHC(O)R^{10}$, -$C(O)NR^{11}R^{12}$ or -$COOR^{12a}$;

R^4, R^5, R^6, R^7 and R^8 each independently represent a hydrogen atom or a C_1-C_6 alkyl group;

t is 0, 1 or 2;

each R^9 independently represents halogen, cyano, hydroxyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, or C_1-C_6 alkyl optionally substituted by at least one substituent selected from carboxyl and C_1-C_6 alkoxycarbonyl;

R^{10} represents a group C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_6 cycloalkyl, adamantyl, C_5-C_6 cycloalkenyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each of which may be optionally substituted by one or more substituents independently selected from nitro, hydroxyl, oxo, halogen, carboxyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylcarbonyl, C_1-C_6 alkoxycarbonyl, phenyl and -NHC(O)-R^{13}, or

R^{10} represents a group $-NR^{14}R^{15}$ or $-O-R^{16}$;

R^{11} and R^{12} each independently represent (i) a hydrogen atom, (ii) a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted with at least one substituent selected from halogen, methyl and trifluoromethyl, or (iii) a C_1-C_6 alkyl group optionally substituted by at least one substituent selected from halogen, amino, hydroxyl, trifluoromethyl, carboxyl, C_1-C_6 alkoxycarbonyl and a 3- to 6-membered saturated or unsaturated ring optionally comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring being optionally substituted with at least one substituent selected from halogen, methyl and trifluoromethyl, or

R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocyclic ring optionally further comprising a ring oxygen atom, the heterocyclic ring being optionally substituted with at least one substituent selected from hydroxyl and C_1-C_6 alkoxy;

R^{12a} represents a hydrogen atom or a C_1-C_6 alkyl group;

R^{13} represents a C_1-C_6 alkyl, amino or phenyl group;

R^{14} and R^{15} each independently represent a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10}, or

R^{14} and R^{15} together with the nitrogen atom to which they are attached form a 4- to 7-membered saturated heterocycle; and

R^{16} represents a hydrogen atom, or a group C_1-C_6 alkyl, phenyl or a saturated or unsaturated 5- to 10-membered heterocyclic ring system comprising at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted as defined above for R^{10};

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1, wherein X and Y have the meanings shown in the following table:

X	Y
bond	O
O	bond
CH_2	O
O	CH_2
C(O)	O
O	C(O)
CH_2	CH_2
-CH=C(CH_3)-	

3. A compound according to claim 1 or claim 2, wherein Z represents a bond, -O- or -CH_2-.

4. A compound according to any one of claims 1 to 3, wherein R^3 represents -NHC(O)R^{10}.

5. A compound according to any one of claims 1 to 4, wherein t is 0 or 1.

6. A compound according to any one of claims 1 to 5, wherein each R^9 independently represents halogen, hydroxyl, C_1-C_4 alkoxy or C_1-C_4 haloalkyl.

7. A compound according to claim 1 selected from:

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-[2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-5-(trifluoromethyl)phenyl]acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-cyclopropyl-4-methoxybenzamide,

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(5-Chloro-2-{[(2S)-3-(6-chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-fluorophenyl)acetamide,

N-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-methoxyphenyl)acetamide,

2-{[(2S)-3-(6-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-fluorobenzamide,

N-(2{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]phenyl)acetamide,

N-(4-Chloro-2-{[(2S)-2-hydroxy-3-(3-oxo-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-Cyclopropyl-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}benzamide,

N-(4-Chloro-2-{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(5-Chloro-2{[(2S)-2-hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-2-hydroxy-2-methyl-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-4-methoxyphenyl)acetamide,

N-[2-{[(2S)-2-Hydroxy-3-(1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)propyl]oxy}-5-(trifluoromethyl)phenyl]acetamide,

N-(2-{[(2S)-2-Hydroxy-3-(2-methyl-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-3-(2,3-Dihydro-1'*H*-spiro[indene-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-(2-{[(2S)-2-Hydroxy-3-(2-oxo-1'*H*-spiro[1-benzofuran-3,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide,

2-{[(2S)-3-(5-Chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-N-methylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxy-*N*-methylbenzamide (trifluoroacetate),

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxy]oxy}-4-hydroxy-*N*-methylbenzamide,

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(2-{[(2*S*)-3-(5-Chloro-1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)-2-hydroxy-2-methylpropyl]oxy}-4-hydroxyphenyl)acetamide trifluoroacetate,

N-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate,

N-(4-Hydroxy-2-{[(2*S*)-2-hydroxy-2-methyl-3-(1'*H*-spiro[1,3-benzodioxole-2,4'-piperidin]-1'-yl)propyl]oxy}phenyl)acetamide trifluoroacetate,

N-(2-{[(2S)-3-(5-Chloro-1'H,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)-2-hydroxy-2-methoxypropyl]oxy}-*N*-cyclopropyl-4-hydroxybenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-(2-hydroxyethyl)benzamide,

N-(2-Aminoethyl)-2-{](2S)-3-(5-chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzamide,

2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

N-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxyphenyl)acetamide,

N-(2-{[(2S)-3-(5-Fluoro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}phenyl)acetamide,

N-[2-({(2S)-3[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide,

N-[2-({(2S)-3[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)phenyl]acetamide,

N-[2-({(2S)-3-[(2S)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide,

N-[2-({(2S)-3-[(2R)-5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl]-2-hydroxypropyl}oxy)-4-methoxyphenyl]acetamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,3'-pyrrolidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxy-*N*-methylbenzamide,

2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoic acid (trifluoroacetate),

3(S)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

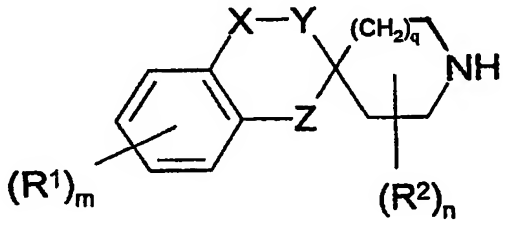
3(R)-1-(2-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-hydroxybenzoyl)pyrrolidin-3-ol,

3-{[(2S)-3-(5-Chloro-1'*H*,3*H*-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-(morpholin-4-ylcarbonyl)phenol,

and pharmaceutically acceptable salts and solvates of any one thereof.

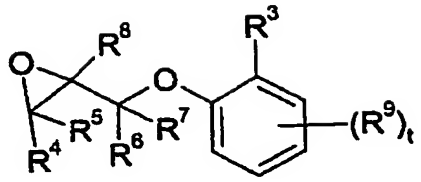
8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 which comprises,

(a) reacting a compound of formula



(II)

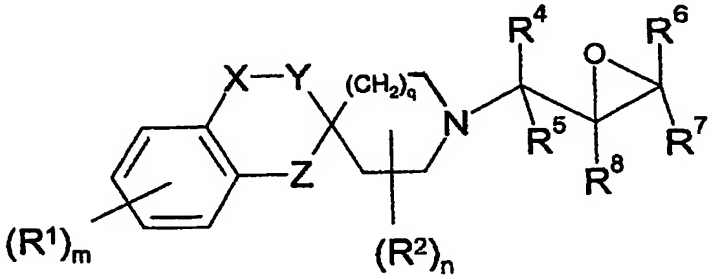
wherein m, R^1, n, R^2, q, X, Y and Z are as defined in formula (I), with a compound of formula



(III)

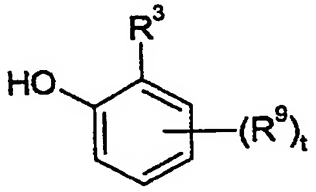
wherein R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

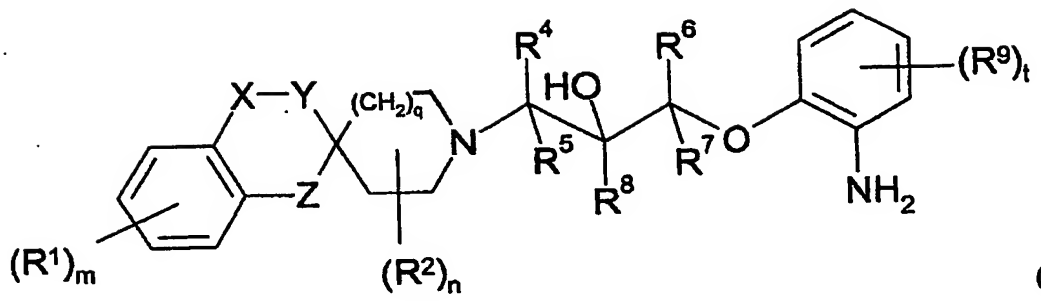
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7 and R^8 are as defined in formula (I), with a compound of formula



(V)

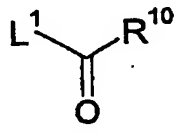
wherein R^3, t and R^9 are as defined in formula (I), in the presence of a suitable base; or

(c) when R^3 represents -NHC(O)R^{10}, reacting a compound of formula



(VI)

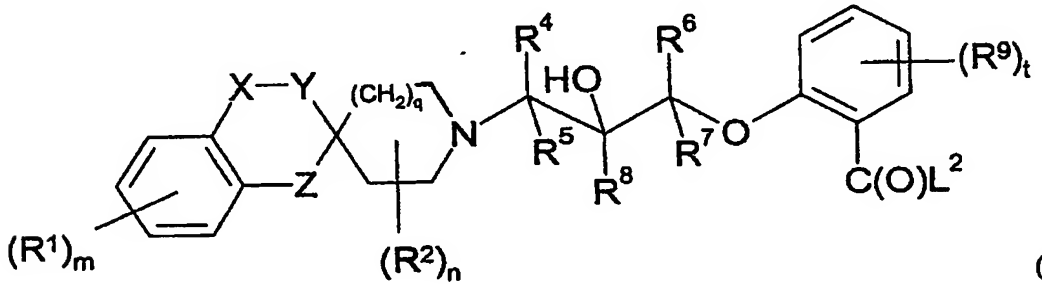
wherein m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in formula (I), with a compound of formula



(VII)

wherein L^1 represents a leaving group and R^{10} is as defined in formula (I); or

(d) when R^3 represents $-C(O)NR^{11}R^{12}$, reacting a compound of formula



(VIII)

wherein L^2 represents a leaving group and m, R^1, n, R^2, q, X, Y, Z, R^4, R^5, R^6, R^7, R^8, t and R^9 are as as defined in formula (I), with a compound of formula (IX), $NHR^{11}R^{12}$, wherein R^{11} and R^{12} are as defined in formula (I);

and optionally after (a), (b), (c) or (d) forming a pharmaceutically acceptable salt or solvate.

9. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

10. A process for the preparation of a pharmaceutical composition as claimed in claim 9 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I) or a pharmaceutically-acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 for use in therapy.

12. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity is beneficial.

13. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating rheumatoid arthritis.

14. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.

15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating asthma.

16. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7 in the manufacture of a medicament for use in treating multiple sclerosis.

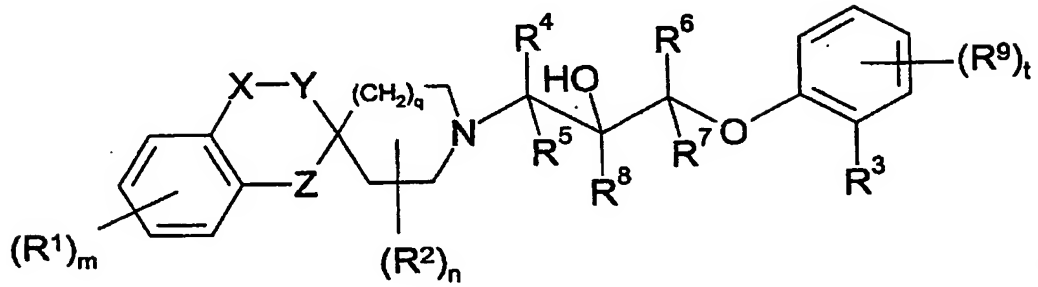
17. A method of treating an inflammatory disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7.

18. A method of treating an airways disease which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 7.

ABSTRACT

NOVEL COMPOUNDS

The invention provides compounds of formula



(I)

wherein m, R^1, n, R^2, q, X, Y, Z, R^3, R^4, R^5, R^6, R^7, R^8, t and R^9 are as defined in the specification, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.